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KETONIC AND NON-KETONIC ESTROGENS *

By W. W. WESTERFELD and EDWARD A. DOISY, *St. Louis, Missouri*

INTRODUCTION

ACTIVE experimental work on the internal secretion of the ovary began with the demonstration of Knauer [1] in 1899 that transplantation of the ovary from its normal site did not produce atrophy of the uterus. Following these experiments many other investigators have made important contributions to our knowledge in this field. Adler,[2] Fellner,[3] Hermann,[4] Frank [5] and others prepared extracts which were active in producing growth of the uterus.

Two other investigations played an important rôle in the development of this field. The first was the introduction (Allen and Doisy [6]) of the accurate and convenient method of assay by the vaginal smear reaction of rats and mice. The second was the discovery of Aschheim and Zondek [7] of the great concentration of estrogenic substances in the urine of pregnant women and mares.

The chemist, supplied with a rapid bioassay procedure and an abundant source of material, lost little time in showing his appreciation. Within the two years following the discovery of Ascheim and Zondek two pure crystalline estrogens were isolated from human pregnancy urine. The isolation in 1929 of the first crystalline estrogen was followed by a deluge of crystalline compounds with estrus producing properties until now some six or seven well characterized compounds have been isolated.

Only two of these estrogens, theelin and theelol, have been obtained from human urine. Although we have examined large quantities of human urine for other estrogens our experiments are thus far unsuccessful. On the other hand, the urine of pregnant mares contains at least six pure estrogens which have been isolated due mainly to the efforts of Girard [8] and of Wintersteiner and Schwenk.[9] Curiously enough in spite of this large number, no theelol has been detected.

With the sole exception of the estriol obtained from human placenta (Browne [10]) no other pure estrogen had been obtained from mammalian

* Read at the St. Louis meeting of the American College of Physicians, April 19, 1937.
From the Biochemistry Department, St. Louis University School of Medicine, St. Louis.

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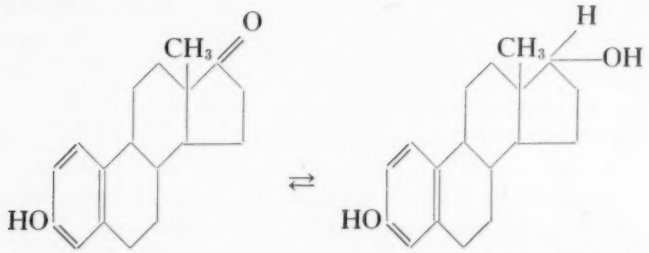
tissues until in 1934 the question of the identity of the follicular hormone attracted our interest. We (MacCorquodale, Thayer and Doisy [11]) expected to find theelin but instead obtained a reduction product of theelin, dihydrotheelin. Some of our findings may be of interest. About four tons of sow ovaries were extracted and the extract purified. Calculated as dihydrotheelin only about 25 mg. were present in the four tons, a relationship of 1 part per 150,000,000. Approximately one half of the activity was recovered in a pure condition and the compound fully characterized. Recently, we have obtained good evidence of the existence of another estrogen in liquor folliculi of sow ovaries.

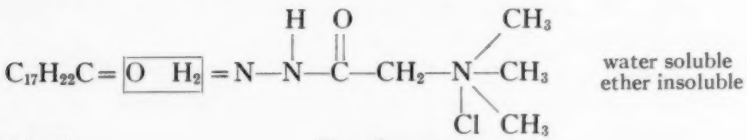
Chemically, the natural estrogens are closely related compounds which are derivatives of the cyclopentanophenanthrene ring systems. All are phenols and in addition each contains an alcoholic or ketonic radical. In our recent work we have applied methods to the study of the occurrence of the ketonic and non-ketonic estrogens. The formulas illustrate the relationship of these two forms.



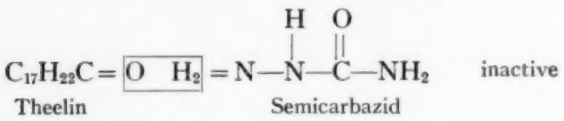
Theelin (ketonic) Dihydrotheelin (non-ketonic)

Using Girard's [12] reagent which reacts with ketones to render them soluble in water and insoluble in ether it seemed that it might be possible quantitatively to separate the ketones from the alcohols as they occur in organs or in excreta.

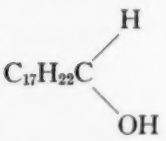
Reactions of Theelin with Girard's Reagent and Semicarbazid



Theelin Girard's reagent



Theelin Semicarbazid



Dihydrotheelin

no reaction with Girard's reagent or semicarbazid—soluble in ether, insoluble in water

Experimental

Studies of mixtures of theelin and dihydrotheelin of known composition enabled us to apply Girard's reagent to quantitative work. Our data (table 1) lead us to believe that the separation is fairly accurate, but that the most likely error is in the possibility of obtaining low values for the ketonic fraction. Furthermore, confirmation of the results for the ketonic fraction can be obtained by treating this fraction with semicarbazid. This treatment causes the loss of at least 98 per cent of the activity of theelin.

Table I

Control of Methods

Substance tested	Rat units of non-ketonic recovered	Rat units of ketone recovered
1. 0.436 mg. theelin (870 R.U.)	<3	865
2. 0.0425 mg. dihydrotheelin (720 R.U.)	700	<5
3. Urine extract containing 300 R.U. dihydrotheelin plus 180 R.U. theelin	360	130
After semicarbazid treatment	350	<11
4. Urine extract containing 300 R.U. dihydrotheelin plus 250 R.U. theelin	350	210
After semicarbazid treatment	340	—

Having worked out satisfactory methods for the quantitative separation of the ketonic from the non-ketonic estrogen, we investigated two interesting points: 1. the distribution of the two forms in ovaries and placenta; and, 2. the transformations that occur after the administration of pure theelin or dihydrotheelin.

Ketonic Estrogens in Tissues

Sow ovaries, from which the liquor folliculi and corpora lutea had been removed, were extracted with boiling ethyl alcohol. Purification was effected by methods commonly used in our laboratory. Upon fractionation between ketonic and non-ketonic estrogens it was found that a small but definite quantity of ketonic estrogen is present (table 2). This finding was confirmed by treatment with semicarbazid which destroyed the estrogenic property of the ketone.

Table II

Estrogens in Ovaries and Placenta

Tissue	Total rat units	Non-ketonic rat units	Ketonic rat units
Sow ovaries after aspiration of liquor folliculi and removal of corpora lutea	320	300	15
Cow ovaries after removal of corpora lutea	350	350	<5
Human placenta		600	200

Using the same methods, the study of cows' ovaries gave no evidence of the existence of a ketonic form, thereby adding one more item to species differences observed in studies of the follicular hormone.

In spite of all of the chemical investigations of human placenta, there is no report of the isolation of any estrogen other than theelol. The extract of 10 placentas was purified. On a per kilo basis, the placenta contained about 800 rat units, of which approximately ¼ (200 R.U.) was ketonic. Since theelin is the ketonic estrogen in human pregnancy urine, probably theelin occurs in placenta. We expect to continue our work on human placenta with the purpose of isolating this ketone in crystalline form.

The Transformation of Estrogens in the Monkey

The development of the methods of separation of estrogens enabled us to study the transformations that occur in the organism. A common biochemical procedure in studying the metabolism of a compound is the administration of enough of the substance under investigation to exceed the destructive capacity of the organism thereby leading to the excretion of the original and intermediate products. The work of Zondek,[13] of Mazer and and Israel[14] and others has shown that a large proportion of estrogens is destroyed or at least disappears and does not appear in the urine as estrus producing compounds. It was found that 3 mg. of dihydrotheelin and 6 mg. of theelin produced an excretion of sufficient quantities of estrogens for our study.

The disappearance of administered estrogens has led us to speculate on the organs in which destruction or transformation occurs. Since the estrogens exert specific effects in the female genitalia a natural supposition is that the hormones might be altered in those organs. Consequently, we have used for our study a normal adult female, an ovariectomized and an ovariectomized-hysterectomized monkey. It appears from our data in tables 3 and 4 that the destruction as measured by the excretion is not due to either the ovaries or uterus.

Each of the monkeys was injected for six consecutive days with the estrogen dissolved in oil. In the case of dihydrotheelin 0.5 mg. was administered daily; in the experiment with theelin each monkey received 1 mg. daily. Collection of urines by the use of metabolism cages was started on the day that the injections were begun and continued for ten days. Urines were collected over chloroform and each daily specimen was stored in the refrigerator until the experiment was terminated.

To effect the complete removal of estrogens the combined 10 day specimen was hydrolyzed with hydrochloric acid and extracted with ether. The ether solution was purified in the usual way and the separation of ketonic from non-ketonic estrogens carried out by the procedure already mentioned.

TABLE III

Estrogens Excreted after the Administration of 3 mg. Dihydrotheelin

Type of monkey studied	Non-ketones excreted (rat units)		Ketones excreted (rat units)		Ratio of R.U. non-ketones to ketones	Total excretion calculated as dihydrotheelin	
	Total	After semicarbazid	Total	After semicarbazid		Mg.	%
Normal	250	225	200	<11	1.25	0.115	3.8%
Castrate *	160	130	70	<11	2.30	0.045	1.5%
Castrate Hysterectomized	290	250	175	<11	1.60	0.105	3.5%

* Loss of some urine suspected.

TABLE IV

Estrogens Excreted after the Administration of 6 mg. Theelin

Type of monkey studied	Non-ketones excreted (rat units)		Ketones excreted (rat units)	Ratio of R.U. non-ketones to ketones	Total excretion calculated as theelin	
	Total	After semicarbazid			Mg.	%
Normal	200	175	300	0.67	0.162	2.7%
Castrate	210	200	200	1.00	0.112	1.97%
Castrate Hysterectomized	275	250	600	0.46	0.317	5.3%

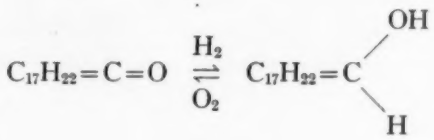
Study of table 3 shows that from 1.5 to 3.8 per cent of the dihydrotheelin was eliminated in the urine. Of these quantities a fair proportion was ketonic, the ratios of non-ketonic to ketonic in terms of rat units being from 1.25 to 2.30.

Turning now to the data obtained following the injection of 6 mg. of theelin, we find a slightly larger quantity of estrogen in the urine. In this case from 2 to 5.3 per cent of the theelin was eliminated as estrogenic material, of which a fair percentage was present in a non-ketonic form, presumably dihydrotheelin. A larger proportion of ketone was present in this experiment possibly due to the administration of twice as much estrogen.

We realize that our results with the normal monkey may be complicated due to the possibility of estrogen being formed in its ovaries. However, it is improbable that this animal produced much estrogen since the results on its urine are quite similar to those obtained on ovariectomized monkeys. This similarity of data also leads to the conclusion that the ovaries, uterus and tubes have very little influence on the excretion of administered estro-

gens. It seems probable that other organs must play an important rôle in the transformation of estrogens.

Our data indicate quite clearly that dihydrotheelin is convertible into a ketonic estrogen and that theelin, a ketone, is converted into a non-ketonic form. Although the evidence is not complete our data indicate that the reaction between theelin and dihydrotheelin is reversible in the monkey.



Summary

By the application of Girard's reagent to the quantitative separation of ketonic from non-ketonic estrogens the following observations were made:

1. A ketonic estrogen is present in sow ovaries.
2. One-fourth of the estrogens in human placenta is ketonic.
3. The existence of a ketonic estrogen in cow ovaries is doubtful; if present, the concentration is less than 5 units per kilo.
4. When dihydrotheelin is injected into a normal adult, a castrate, or a castrate-hysterectomized monkey, 30 to 45 per cent of the excreted estrogenic activity is ketonic.
5. When theelin is injected into a normal adult, a castrate, or a castrate-hysterectomized monkey, 30 to 50 per cent of the excreted estrogenic activity is non-ketonic. The evidence indicates that in the monkey the reaction between theelin and dihydrotheelin is reversible and that the ovaries and uterus are not essential for this transformation.

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TREATMENT OF DIABETES MELLITUS WITH INSOLUBLE INSULIN COMPOUNDS

II. HISTONE–INSULIN *

By P. A. Gray, M.D., F.A.C.P., Fritz Bischoff, Ph.D., and W. D. Sansum, M.D., F.A.C.P., *Santa Barbara, California*

Throughout the past two years we have been studying the effect of insoluble insulin compounds in the treatment of human diabetes mellitus. The clinical results obtained with insulin tannate and insulin-zinc compounds have already been reported.[1] This communication deals with our clinical trial of the histone-insulin compound discovered and prepared for clinical use by one of us (F. B.[2]). This preparation has been found capable of controlling diabetes when used alone. Because of its slow and prolonged action on the blood sugar it is particularly useful in severe types of diabetes in juvenile patients and in elderly cases with cardiovascular complications.

Histone

The histones are one of a group of seven simple proteins, the others being the albumins, globulins, glutelins, prolamines, albuminoids and protamines. They are not coagulable by heat and although soluble in water and dilute acids, they are insoluble in ammonia, a feature which is characteristic. In common with the other five simple proteins and in contrast to the protamines they consist of a large number of amino acids. (Table 1.)

Table I

Chemistry of Protamine and Histone

	Protamine	Histone
Per cent nitrogen	25–30	17
Per cent histidine	Free	5
NH_4OH	Soluble	Precipitated
Sulphur	Absent	Present
Per cent amino acids—		
Glycine	0	0.5
Alanine	0	3.5
Leucine	0	11.8
Proline	11	1.5
Phenylalanine	0	2.2
Glutamic acid	0	3.6
Tyrosine	0	5.2
Arginine	87	15.5
Lysine	0	6.9

* Presented at the St. Louis meeting of the American College of Physicians, April 22, 1937.

From the Chemical Laboratories of the Santa Barbara Cottage Hospital and the Sansum Clinic, Santa Barbara, California.

The histone which was used clinically was prepared by the method of Kossel and Kutscher as modified by Bischoff [2] to reduce the ash content. This ash contains calcium and magnesium. Unknown constituents present in the material used clinically are less than 1 mg. per 2500 units of insulin. Thymus glands, C. P. hydrochloric acid, ammonia water, alcohol and ether are the only substances required in the preparation of the histone.

The histone is added to commercial insulin at the acid side of the isoelectric point of insulin to form a solution. To this is added a disodium phosphate buffer solution which precipitates the histone-insulin on the alkaline side of the insulin isoelectric point. The pH of the solution at the time of injection approximates 6.7. The precipitate is finely divided and readily forms a suspension on shaking. A glass bead has been placed in the sterile, rubber capped vials to facilitate uniform mixture before injection.

Zinc and other metals of the H_2S group are definitely absent from the histone preparations which we have used. The only possible source of zinc would be from the commercial insulin used in the preparation of the combination.

Material

To date histone-insulin has been used clinically on 30 patients under controlled conditions. These patients have varied in age from 5 to 74 years and present all grades of severity of diabetes mellitus. All were hospitalized during part of the period of observation. Three of these patients have taken histone-insulin for the past three months consecutively. Sporadic observations are available on five additional patients.

Technic of Administration

Histone-insulin is injected subcutaneously with the ordinary syringe and needle into the same areas of the body as is commercial insulin. In several hundreds of injections only once has any local tissue reaction been noted at the site of injection. This consisted in an ephemeral erythema. No painful subcutaneous lumps have been encountered. Wells [3] did not characterize histones as being allergenic. No patient has yet experienced any inconvenience from the injections, even of volumes up to 1.6 c.c. (of a U–50 strength).

When histone-insulin has been used alone to control a patient's diabetes one dose in 24 hours has usually sufficed. This dose is given either one-half hour before or immediately after breakfast. A few patients have required two doses in 24 hours. They have received three-quarters of the total dose after breakfast and one-quarter immediately before supper. Some patients have required a small dose of commercial insulin together with their daily dose of histone-insulin. This has been injected at the same time as the new preparation but with a separate syringe and into a different area of the body.

We recommend that the solution of histone-insulin be kept cool and that

it be shaken vigorously prior to each injection to insure uniform suspension of the insoluble insulin throughout the solution. The preparation used has been reasonably stable.

Results

The observations of Bischoff [2] that histone delays the absorption and prolongs the hypoglycemic action of commercial insulin have been confirmed in man. Figure 1 shows this effect. Under identical experimental conditions this diabetic patient's blood sugar level remained low for a longer period of time after a single injection of histone-insulin than after regular insulin.

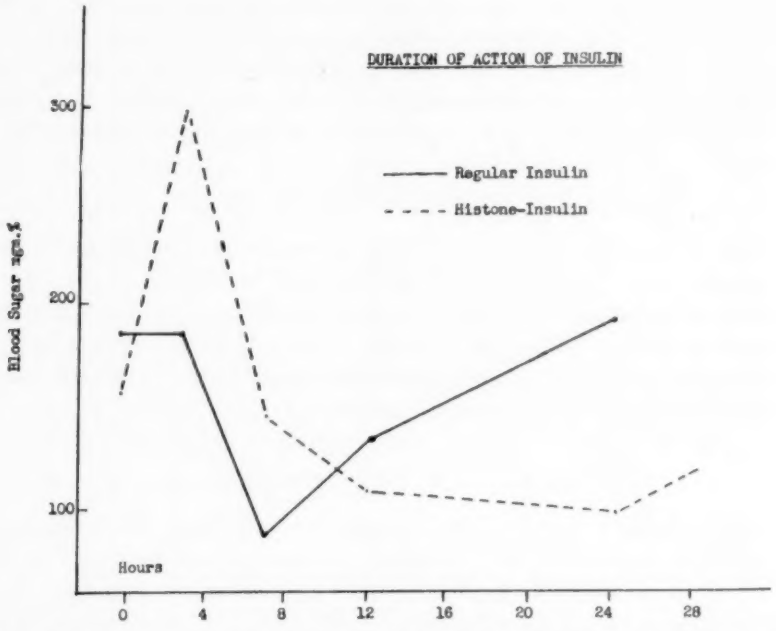

Fig. 1. M. B. A comparative study of the duration of action of regular insulin and histone-insulin in a diabetic male aged 24. On each test day the patient remained at bed rest. Forty units of insulin were given. One-half hour later he ate a breakfast containing C 97, P 27, F 44 and then fasted for the remainder of the test period. Evidence is presented that histone-insulin is absorbed more slowly, but acts over a much longer period than regular insulin.

In another group of experiments the physiologic effects of single doses of commercial insulin, protamine-insulin (zinc) [4] and histone-insulin were compared on the same patient. The general plan of the experiments was as follows: Each subject ate the same food each test day at the same hour and either remained at bed rest or exercised uniformly. Each test day was separated from the others by a rest period of at least 24 hours. This was felt to be especially essential between the days on which the insoluble compounds were given in order to avoid any accumulative effect. Under the conditions

of the experiments where food was taken at regular intervals the blood sugar level reached its lowest point after a single injection of commercial insulin in four to four and a half hours, and after about ten hours had returned to the fasting level. In the case of both protamine-insulin (zinc) and histone-insulin the lowest point was reached between 14 and 24 hours after the injection.

Table 2 records the effect observed in a diabetic male aged 27. Food was served six times during the day, at 7:00 and 10:00 a.m., 12:00 m, 3:00, 6:00 and 8:00 p.m. as indicated. One half hour before breakfast 45 units of insulin were given subcutaneously. Blood sugar levels were determined before the insulin was given and at three, five, seven and a half, eleven and a half, 15 and 24 hours thereafter. Urine was collected separately from 6:30 a.m. to 9:00 p.m. and from 9:00 p.m. to 7:00 a.m. the following morning. On the test day when regular insulin was given there

TABLE II

Time	Food			Blood Sugar (mg. %)	Urine Sugar (gm.)	Blood Sugar (mg. %)	Urine Sugar (gm.)	Blood Sugar (mg. %)	Urine Sugar (gm.)
	C.	P.	F.						
6:30 a.m.				160		158		156	
7:00	48	28	23	Insulin (45-U)		Protamine (45-U)		Histone (45-U)	
9:30				84		244		268	
10:00	10	0	0						
11:30				54		188		192	
12:00 m.	47	28	23						
2:00 p.m.				150		190		174	
3:00	15	2	0						
6:00				240		124		154	
6:00	42	29	26						
8:00				206	8.9	78	0	120	15.3
7:00 a.m.						100	3	170	0

was no postprandial rise in the blood sugar after breakfast. The blood sugar reached its lowest level five hours after the injection, after which it rose. On both days when the insoluble insulin compounds were given there was a definite postprandial rise after breakfast with a subsequent gradual fall even though the patient continued to eat at the usual times. In the case of protamine-insulin (zinc) this secondary fall was more rapid than with histone-insulin. This difference was probably due to difference in the rate of absorption of the two compounds. Since the subject's blood sugar remained higher for a longer period of time after histone-insulin than after protamine-insulin (zinc), it was to be expected that a greater amount of sugar would be found in the first 12 hour urine specimen on this day. The lowest level of the blood sugar after both of the insoluble compounds was not reached until 15 hours after their injection.

Table 3 records another experiment of the type just described in a diabetic woman aged 53. In this case again the lowest level of the blood sugar after commercial insulin was reached five hours after the injection. After protamine-insulin (zinc) the blood sugar rose after breakfast to fall gradually, reaching its lowest level 24 hours later. After histone-insulin the post-breakfast rise did not occur, presumably because in this instance some free insulin was present in the mixture injected. The smaller amount of sugar present in the night collection of urine noted on each test day when the insoluble-insulin compounds were given suggests continued action, that is absorption of the compound, during the night.

TABLE III

Time	Food			Blood Sugar (mg. %)	Urine Sugar (gm.)	Blood Sugar (mg. %)	Urine Sugar (gm.)	Blood Sugar (mg. %)	Urine Sugar (gm.)
	C.	P.	F.						
6:30 a.m.				46		76		52	
7:00	56	21	33	Insulin (40-U)		Protamine (40-U)		Histone (40-U)	
11:30				52		276		124	
12:00 m.	42	24	27						
5:00 p.m.				252		248		180	
6:00	59	40	24						
9:00	18	2	0						
10:00				412	14.6	332	17.6	344	24.5
7:00 a.m.				300	88.4	192	18.2	230	16.3

Table 4 records another similar experiment in a diabetic male aged 74. Here again the delayed absorption and prolonged hypoglycemic action of the insoluble-insulin compounds as contrasted to regular insulin is apparent. As in the preceding two experiments the subject's blood sugar level 24 hours after a single injection was not quite so low after histone-insulin as after protamine-insulin (zinc).

TABLE IV

Time	Food			Blood Sugar (mg. %)	Urine Sugar (gm.)	Blood Sugar (mg. %)	Urine Sugar (gm.)	Blood Sugar (mg. %)	Urine Sugar (gm.)
	C.	P.	F.						
7:00 a.m.				180		196		202	
7:30				Insulin (30-U)		Histone (30-U)		Protamine (30-U)	
8:00	56	14	18						
11:30				88		228		296	
12:00 m.	42	36	29						
5:00 p.m.				166		202		222	
6:00	53	28	29						
8:30	18	7	8						
10:00				320	0	346	Trace	276	5.8
7:00 a.m.				216	4.5	178	Trace	124	0

In all our experiments of this type some action on the blood sugar has been noted 24 hours or more after a single injection of the insoluble compounds. Although individual patients have shown some variation, protamine-insulin (zinc) and histone-insulin have, in general, behaved similarly.

Prior to using histone-insulin the 30 patients upon whom we have sufficient data required 2.7 average injections of commercial insulin daily, while on the new compound 1.2 average injections have sufficed to maintain a comparable degree of control. Various patients have received histone-insulin from a few days to three months continuously. Certain patients have received it intermittently over a year. We have studied principally a group of severe cases, many of them children, because it is obvious that in a high-dosage case requiring multiple injections daily a slow acting insulin would be most useful. Furthermore such cases have been the ones most available to us for such study. The ensuing protocols will show that in addition to reducing the numbers of injections required daily, the histone-insulin has reduced the fluctuations in the patients' blood sugar levels from one part of the day to another. In certain mild cases the effect of a single dose has apparently lasted throughout 48 hours. Recently we have carried several patients through both major and minor surgery by giving them daily injections of histone-insulin supplemented by small amounts of commercial insulin.

Histone-insulin and protamine-insulin (zinc) have had the same relative effect on this group of patients. Certain patients have been changed from one to the other easily with only minor readjustments. Some who have not been satisfactorily controlled with one of these new compounds have been with the other. The principal difference noted thus far in their clinical effect has been in the frequency of hypoglycemic reactions the morning of the day following the injection. Such reactions have been somewhat more frequent with protamine-insulin (zinc) than with histone-insulin. The recent review of the literature on protamine-insulin by Wilder [5] makes further discussion of this preparation unnecessary.

Hypoglycemic Reactions

In appropriate dosage histone-insulin is capable of inducing characteristic hypoglycemic reactions. These usually appear 24 hours after a single injection and coincide with the peak of the depression of the blood sugar. Since the histone-insulin is injected just before or after breakfast, reactions have usually occurred at a corresponding time the ensuing morning.

The mildness of somatic manifestations is noteworthy. Sweating and trembling have been seen rarely. Drowsiness, headache and dizziness are the principal symptoms. Children have, on occasion, been hard to awaken and when finally awake have complained only of headache. We have occasionally seen children who presented no external manifestation of any kind

and who seemed to be sleeping naturally, at a time when their blood sugar was at shock level.

Relief of hypoglycemic shock has been accomplished in the same manner as after commercial insulin. This difference, however, is worthy of note. Whereas a single dose of readily available carbohydrate usually suffices in the case of regular insulin, repeated doses may be required after histone-insulin, due to late and continued absorption. This phenomenon has been seen in hypoglycemic shock produced by other insoluble insulin compounds.

Comment

In this study we have been concerned primarily with determining the rôle of histone-insulin in the treatment of human diabetes mellitus. Its ability to replace regular insulin as an agent in controlling diabetes has been demonstrated. Considerable individual variation has been noted among the patients studied. In the majority an adequate degree of control has been attained with one dose each 24 hours. Some cases which could not be controlled on one dose have been controlled on two doses. A few others could not be adequately controlled with any practical dosage scheme; these patients have discontinued taking histone-insulin and have resumed regular insulin. In every case studied we have tried to effect control of glycosuria with one dose in 24 hours, or a combined dose of new and regular insulin taken simultaneously. When this has not been possible patients, as a rule, have preferred to return to two (in some cases even three) injections of regular insulin than to continue with the same number of injections of the new preparation.

A control group of patients comparable in number and severity of diabetes to those receiving histone-insulin have been given protamine-insulin (zinc). Our clinical impression at present is that the two groups have behaved quite similarly. Histone-insulin and protamine-insulin (zinc) each have yielded good results in some patients and not in others. They both delay the absorption of insulin. The same patient can be controlled with either preparation and changed from one to the other with only minor adjustments of unitage. Thus far three patients have experienced distressing local reactions at the site of injection of protamine-insulin (zinc), sufficient to warrant the discontinuance of the preparation. None such have been encountered with histone-insulin. Some patients whose diabetes could not be controlled with one dose in 24 hours of one preparation have been controlled satisfactorily when changed to the other.

Our experience with histone-insulin to date has been too limited to warrant any statement concerning the glucose value of one unit of the new insulin compared to that of the old. Some patients in this group have required fewer total units of histone-insulin than of regular insulin on the same diet; the majority have required about the same number and some have required more.

Our records show considerable daily variation in the amount of glycosuria and the level of the blood sugar in those patients whose blood sugar on regular insulin rises during the night. Since the action of histone-insulin is comparable to that of regular insulin [2] when injected intravenously we have assumed that these irregular variations are due to variable absorption on different days. This difficulty is common to all of the insoluble insulin compounds with which we have worked.

Protocols

Case 1. J. G., a male, aged 37, has had diabetes for 15 years and angina pectoris for three years. He has been under continuous observation since May 1934. During this period he has never been consistently sugar free; his insulin has been administered in four doses, varying between 66 and 80 units. Normal fasting blood sugar levels have only been obtained when insulin has been given during the preceding night. Before starting the histone experiment this patient had seldom been free of precordial pain on effort for more than 24 hours at a time between 1933 and 1936. Electrocardiograms taken at various intervals have shown a high take-off and rounding of ST_2 and $_3$ and depression of T_4 below the isoelectric line. The blood pressure has fluctuated between 140 to 150 systolic and 90 to 100 diastolic. It has been demonstrated that this patient would experience anginal pains whenever his blood sugar fell below 100 or rose above 300 mg. per cent. Attacks have been induced at will by inducing fluctuations in his blood sugar and relieved without the aid of vasodilators by restoring the blood sugar to normal.

Table 5 shows that this patient was gradually changed from commercial insulin to histone-insulin. It has sufficed to control his diabetes. One dose per day has replaced four of commercial insulin and effected a comparable degree of control. The number of units of histone now taken daily at one injection approximates those formerly distributed in four. In spite of large volumes of histone-insulin having

Table V

Date	Insulin Units				Urine	Blood Sugar	
		a.m.	m.	p.m.		a.m.	p.m.
5-13-34		40	13	25	13.8		
5-15-34	4	30	13	18	+	325	
3-11-36	7	38	13	18	18.0		
3-14-36	10	38	13	18	+		
11-24-36		23		18			
		5		**10**	62.3	344	
11-30-36		23		13	45.6	332	270
		23					
12-14-36		**51**		**10**	5.0	226	238
1- 7-37		**56**		**10**	52.0		
1-21-37		**55**		**10**	5.0		
2-10-37		**70**			5.0		
2-17-37		**70**			20.0		
3- 1-37		**75**			18.0	280	124
3-22-37		**75**			—		

Diet = C 172, P 83, F 86.
Weight = 143–145 lbs.
Figures in **boldface type** indicate Histone.

been injected over several months' time no local or systemic reactions have been encountered. The only clinical manifestation of hypoglycemic shock has been headache and dizziness. Since taking histone-insulin this patient has not experienced anginal pain at any time (now over two months), in spite of the fact that his blood sugar level has occasionally attained that known previously to induce an attack. A recent electrocardiogram has been reported to be negative.

Case 2. P. R., a boy, aged 14, has had diabetes for five years and has been under continuous observation during this time. On a maintenance diet his 24 hour urine specimens have usually been sugar free. His daily insulin requirement has been about 57 units, given in four doses, for the past three years.

This patient has been changed over to histone-insulin. As shown in table 6 it has sufficed to control his diabetes satisfactorily when injected once daily. Ten to 20 per cent more units per day have been necessary than formerly. The only clinical manifestation of hypoglycemia has been headache. No local reactions at the site of injection have been noted.

The horizontal divisions of table 6 indicate separate periods of hospitalization. The final one (3–26–37) followed an attack of scabies. Loss of carbohydrate toler-

TABLE VI

Date		Insulin Units a.m.	m.	p.m.	Urine	Blood Sugar a.m.	p.m.
7–30–36	10	18	12	15	+	166	
11–15–36		18		15			
		12		**8**	40.5	440	320
11–21–36		18		15			
		34		**23**	Trace	284	236
11–28–36		**61**			71.7	88	332
12– 5–36		**61**				238	
12–12–36		**62**			−		
12–18–36		**56**			+		
12–27–36		**56**			−	182	196
12–28–36		**56**			29.6	238	246
12–29–36		**56**			−	308	
1–16–37		**62**			−		
2– 7–36		**66**			+		
2–19–37		**70**			−		
3–26–37		**63**			37.8	408	360

Diet = C 208, P 84, F 100.
Weight = 96.5–102.3 lbs.
Figures in **boldface type** indicate Histone.

ance during infections is not prevented by using the new insoluble insulin compounds. This observation has been amply confirmed during the recent epidemic of upper respiratory infections.

This patient has received the largest volume of the histone-insulin preparation. While taking it he has gained in weight, felt well, and exhibited no untoward local or systemic effects.

Case 3. B. A., a diabetic girl, aged 5 years, was admitted to the hospital in diabetic ketosis. One hundred fifty units of insulin were given during the first 24 hours. After recovery from ketosis the patient was controlled on commercial insulin.

Table 7 shows how this patient was changed over to histone-insulin. One month later a smaller total number of units sufficed to control her diabetes than on commercial insulin. She had gained 2 kg. in weight during the period of observation.

TABLE VII

Date	Insulin Units a.m.	m.	p.m.	Urine	Blood Sugar a.m.	p.m.
2-18-37	15	10	15	7.7	274	76
2-21-37	15	10	15	+		
2-22-37	**32**		8	—	236	
2-25-37	**35**		5	—	103	134
3- 7-37	**40**			Trace	108	
3-17-37	**30**			2.6		
3-21-37	**25**			—	354	

Diet = C 145, P 70, F 37, Cal. 1193.
Weight = 13–15 kg.
Figures in **boldface type** indicate Histone.

Once while receiving 40 units of histone-insulin this child went into hypoglycemic shock under conditions which may well occur in other patients on home management. She awoke one morning feeling queerly. Her mother, failing to recognize any unusual behavior, gave the usual dose of histone-insulin a few minutes before breakfast as customary. Before breakfast could be eaten the child was unconscious. When readmitted to the hospital the child exhibited an interesting wave-like response to treatment. For a while after the administration of glucose she would arouse, appear normal, talk rationally, drink orange juice, and then sink back into a stupor. This phenomenon continued for 36 hours, indicating a delayed absorption of the histone-insulin. Recovery was complete with no demonstrable ill effects.

Case 4. S. H., a man, aged 74 years, has had diabetes 18 years. Before using histone-insulin there had been no apparent change in his carbohydrate tolerance for many weeks, and the usual insulin requirement was about 50 units. Throughout the three different periods when he received histone-insulin he was confined to bed on account of vascular changes in the extremities. On each trial ranging from two to four weeks one dose of histone-insulin per day controlled his diabetes. Table 8 gives a synopsis of these three different experimental periods.

TABLE VIII

Date	Insulin Units a.m.	m.	p.m.	Urine	Blood Sugar	Diet C.	P.	F.
1-28-36	**31**	11	11	—		139	80	69
2- 4-36	**27**			5.5	196			
2-11-36	**40**			—	242			
6- 4-36	30		15	—	220	240	77	59
6-14-36	32		**14**	7.6	202			
6-21-36	**30**			Trace	204			
7- 3-36	**35**			—	220			
3-21-37	10	10	10	—		231	82	86
3- 8-37	**35**			—	154			
3-15-37	**35**			—	150			

Figures in **boldface type** indicate Histone.

SUMMARY

Histone-insulin is capable of controlling human diabetes mellitus when used alone. Its action on the blood sugar is more delayed and prolonged

than that of commercial insulin. No local or systemic reactions have been noted even with injection of a large volume or over long periods of time. In a group of 30 patients an average of 2.7 injections of commercial insulin per day has been reduced to an average of 1.2 injections of histone-insulin.

We are indebted to Mr. W. R. Dickinson of Hope Ranch Park, Santa Barbara for a grant to cover the preparation of the histone used in this study and to Eli Lilly and Company for a generous supply of insulin.

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ACACIA THERAPY IN NEPHROTIC EDEMA *

By MICHAEL J. LEPORE,† *Bronx, New York*

DURING the past decade evidence has accumulated from many quarters lending support to the physico-chemical concept of edema formation advanced originally by Starling [1] in 1895. The basis of this theory is that capillary pressure and serum colloid osmotic pressure are opposing forces, the balance between which determines the direction of movement of fluid and of the crystalloidal constituents of the blood across the capillary wall. In view of the numerous excellent papers on the subject, it is needless to review the evidence establishing the validity of the Starling concept in explaining the mechanism of production of nephrotic edema. The lowering in serum albumin concentration and hence in serum colloid osmotic pressure, seen in nephrosis, nutritional edema and similar states is, according to the Starling theory, the major factor determining the incidence of edema in these conditions.

Rational attempts to remove nephrotic edema have, therefore, been aimed at raising the serum colloid osmotic pressure. Transfusions of whole blood, serum or plasma have been used. High protein diets have been given in an attempt to raise serum protein levels by stimulating regeneration of protein. Artificial colloidal substitutes for serum proteins have been proposed, gum acacia being the most popular. Hartman and associates [2] reported favorably on the use of gum acacia in the treatment of nephrosis in children. In five of six cases, they found that when other measures had failed, the intravenous injection of acacia resulted in the initiation of diuresis. They asserted that the aim of acacia therapy is to raise the serum colloid osmotic pressure to a level of about 17 cm. of water, and in this way to reverse the process of transudation so that absorption of edema fluid is favored. Failures they thought were due to insufficient dosage of acacia. They advocated giving doses of one gram of acacia per kilogram of ideal body weight in the form of a 15 per cent solution.

In 1935, Dick and associates [3] recorded discouraging experiences with acacia in the management of nephrotic edema, reporting that acacia was often ineffective in causing diuresis, and that a fall in serum protein concentration and a progressive anemia followed its use. They especially stressed the fact that the decrease in serum protein concentration was of such magnitude as to negate any rise in colloid osmotic pressure produced by the presence of acacia in the serum, the net result being appreciable decreases in the calculated serum colloid osmotic pressure. They reported furthermore

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From the department of Internal Medicine, Duke University School of Medicine, Durham, North Carolina.

† Research Fellow of the American College of Physicians.

that following its intravenous injection acacia could be demonstrated in appreciable concentrations in pleural and peritoneal fluids of their patients. Moreover, while the first course of acacia injections was often effective in relieving edema, subsequent injections proved ineffective. Inspection of their protocols reveals that they used adequate amounts of acacia, for relatively massive dosage was employed.

In support of their clinical observations, Dick and associates reported several experiments on dogs. Four dogs were given acacia intravenously, following which the serum protein concentrations of all four animals decreased considerably. With cessation of the acacia injections, the serum proteins returned to normal. There was a distinct tendency in their experiments for both albumin and globulin fractions to vary in the same proportion. The possibility that these results were dilution effects was dismissed by them without the presentation of adequate evidence in support of their interpretation. They concluded that " the use of acacia intravenously in patients with nephrosis was not found of value and was associated with undesirable results."

It is the purpose of this communication to report four instances of nephrotic edema in adults treated with acacia. Certain of the phenomena reported by Dick and associates [3] were encountered in these cases, but in the light of actual measurements of the plasma volume, it has been possible to interpret them differently. Two cases (Case 3, M. W., and Case 4, Z. R.) fulfilled the classical requirements for the diagnosis of so-called lipoid nephrosis. The other two were definitely cases of chronic active glomerulonephritis in the nephrotic stage.

Methods

The plasma protein analyses were done by the method of Howe.[4] The plasma volume measurements in the first three cases were made with the method of Rowntree and associates [5] as modified by Whipple and associates.[6] There are certain objections to this method which have been considered in some detail in another report.[7] However, experience with an improved technic [7] confirms the general trend of the observations made with the older method and, furthermore, the magnitude of most of the changes to be reported is well beyond the errors inherent in the older method. It has been explained elsewhere [7] that values for plasma or serum volume obtained by the dye method are not absolutely accurate for they include a small volume of lymph. For this reason, in the present report, emphasis has been placed on the *changes* in serum or plasma volume occurring in the same patient rather than upon the actual values obtained.

Determinations of plasma volume were done on patients who had been fasting for three or more hours and were lying flat in bed. In Case 4, the serum volume measurements were made with the improved method.[7]

Acacia in saline (Lilly) was given in the concentrations stated below. On one occasion acacia without saline was used.

Results

Case 1. V. B., white, male, aged 16 years.

History: Admitted to Duke Hospital on October 13, 1934 complaining of "swelling of the face, ankles, and stomach" of one month's duration. The onset of illness was referred to a "cold" which came on shortly after wading in cold water while seining. Swelling of the ankles and puffiness of the eyelids were noted on the day following the onset of the cold. The urine, examined on the fifth day of illness by his doctor, boiled solid. He was placed on a low protein diet with fluids restricted and was given magnesium sulphate by mouth. The edema at first diminished but soon recurred and during the week prior to admission had become progressively worse.

Physical Examination: Blood pressure, 144 mm. of Hg systolic and 110 diastolic. Marked edema of the eyelids is present. There is considerable pre-sacral and pretibial pitting edema. Signs of bilateral pleural fluid and of moderate ascites are elicited. The optic fundi show no exudate or papilledema. The tonsils are considerably enlarged and appear chronically infected. No evidence of cardiac failure is present.

Urine: Specific gravity 1.035, dark brown, albumin four plus. Microscopic: 10 to 12 red blood cells per high power field. Occasional granular cast.

Blood: Hemoglobin 16 grams per 100 c.c. Red blood cells 5,570,000 per cu. mm.

Blood non-protein nitrogen 34 mg. per cent. Total plasma proteins 3.54 gm. per 100 c.c., plasma albumin 0.67 gm. per 100 c.c., plasma globulin 2.87 gm. per 100 c.c., cholesterol 375 mg. per 100 c.c. Wassermann and Kahn reactions negative.

Kidney function tests: Phenol red excretion, 65 per cent excreted in two hours (October 14). Urea clearance, 145 per cent of normal, October 16, 1934 and 95 per cent of normal, October 22, 1934.

Basal metabolic rate: minus 27 per cent (October 16, 1934).

Therapy: The patient was placed on a high protein, salt-free diet and was kept in bed. The edema remained unchanged. On October 20, 1934, he was given intravenously 45 grams of acacia in saline as a 15 per cent solution. At the end of the infusion, slight urticaria appeared and the proximal phalangeal joint of the right index finger appeared tense and swollen. No febrile reaction occurred. The urticaria and joint swelling subsided after the injection of a total of 0.6 c.c. of a 1–1000 solution of adrenalin. This injection of acacia was followed by an almost immediate and persistent large diuresis. Another 30 grams of acacia in saline as a 15 per cent solution were given on October 22, 1934. The further sequence of events is illustrated in figure 1. It is there seen that after the injection of acacia the plasma volume rose markedly and the plasma protein concentration and cell volume fell, presumably as a result of hemodilution. Diuresis continued as shown. This patient was followed at monthly intervals for another six months and during this time remained practically free from edema on an active regime despite the persistence of marked albuminuria and a low serum albumin concentration. Clinically demonstrable hepatic enlargement was at no time present.

Case 2. D. J., colored male, aged 26.

History: Admitted April 9, 1935 with the complaint of "swelling of the body" of two months' duration. His illness began two months before when he first noted the insidious onset of puffiness of the eye-lids and ankles. Smoky urine was also noted at this time. He kept on with his usual activities and the edema soon became generalized. Five weeks after the onset of his initial symptoms, he consulted a

doctor who told him that he had kidney trouble and prescribed a meat-free diet with limited salt. Progressively increasing edema led him to enter the hospital.

The past history reveals the fact that he has had occasional attacks of sore throat. However, he does not remember having had a sore throat with the onset of the present illness. He had a chancre 10 years ago for which he received no antiluetic therapy.

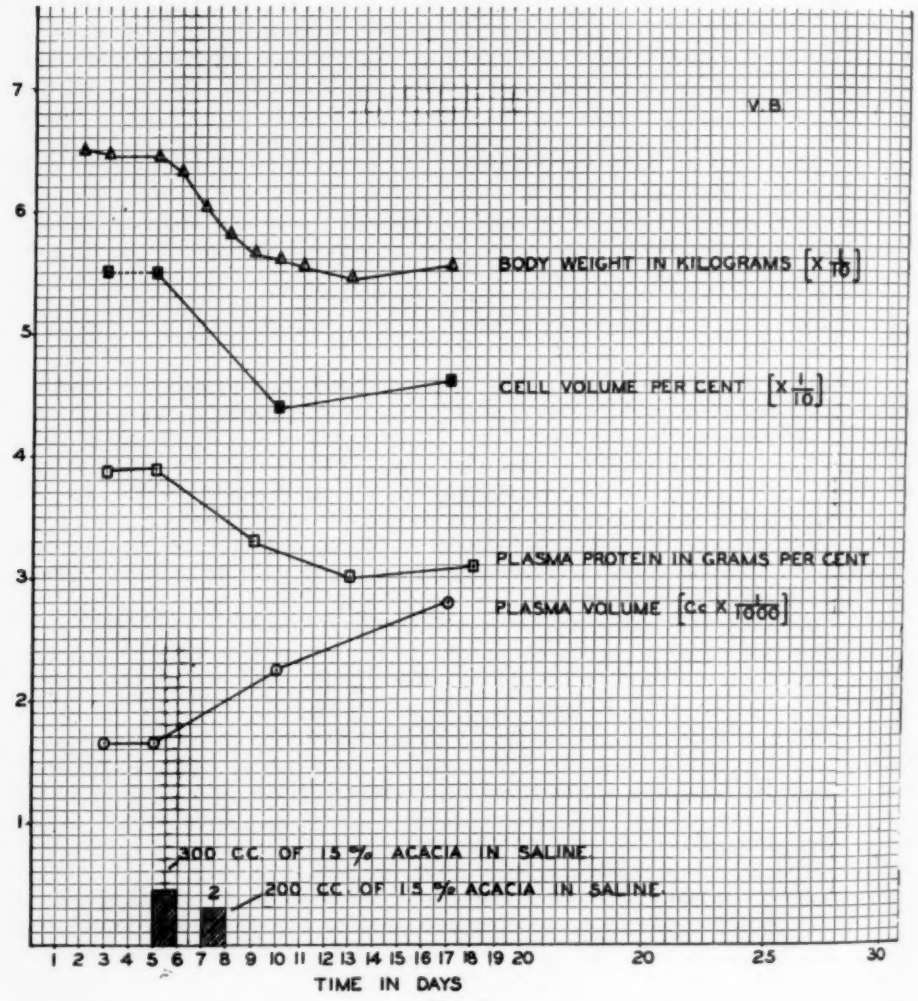
V. B.
BODY WEIGHT IN KILOGRAMS [X 1/10]
CELL VOLUME PER CENT [X 1/10]
PLASMA PROTEIN IN GRAMS PER CENT
PLASMA VOLUME [Cc X 1/1000]
300 CC. OF 15 % ACACIA IN SALINE.
200 CC. OF 15 % ACACIA IN SALINE.
TIME IN DAYS

FIG. 1.

Physical Examination: Blood pressure, 186 mm. of Hg systolic and 90 diastolic. There is considerable edema of the face and hands. A moderate amount of ascites, and pre-tibial and pre-sacral soft, pitting edema are present. The tonsils are moderately enlarged and seem chronically infected. The heart is moderately enlarged to the left and the sounds are forceful. The liver is not palpable. The fundi oculi show slight bilateral papilledema. No exudates are seen.

Urine: Reddish brown, specific gravity 1.016, albumin four plus. Microscopic: Many red blood cells, numerous leukocytes, many coarse granular and hyaline casts.

Blood: Hemoglobin 13.6 gm. per 100 c.c. Red blood cells 3,880,000 per cu. mm. Blood non-protein nitrogen 33 mg. per cent. Total plasma proteins 4.27 gm. per 100 c.c. Plasma albumin 1.44 gm. per 100 c.c. Plasma globulin 2.83 gm. per 100 c.c. Cholesterol 911 mg. per cent. Wassermann and Kahn reactions four plus.

Kidney function tests: Phenol red excretion 65 per cent in two hours. Urea clearance, 51 per cent of normal April 16 and 46 per cent of normal May 8.

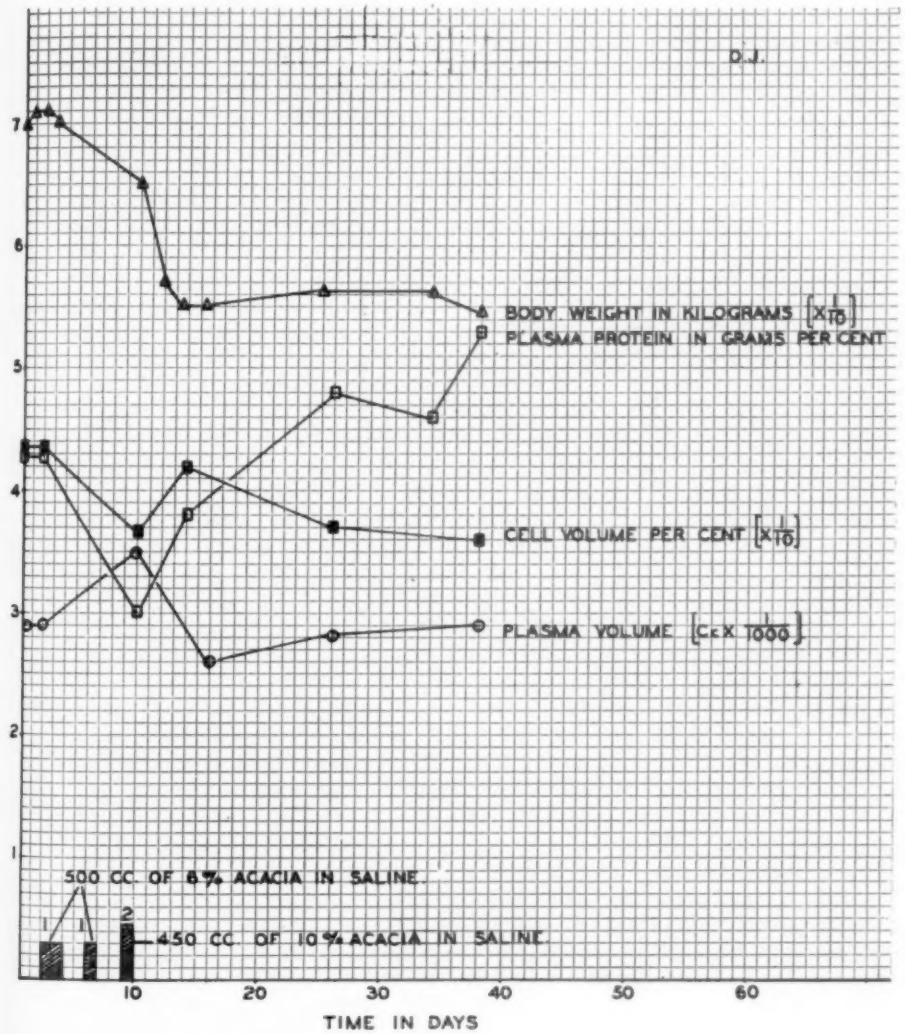

FIG. 2.

Basal metabolic rate, minus 24 per cent (April 11).

Therapy: The patient was placed on a high protein, low salt diet. On April 10, 1935, 500 c.c. of 6 per cent acacia in normal saline were given intravenously, and the dose was repeated on April 11 and April 14. Diuresis occurred immediately after the first dose of acacia and progressed as shown in figure 2. Another 45 gm. of acacia in saline in 10 per cent solution were given on April 17.

Following the acacia injection, as is seen in figure 2, the plasma volume increased considerably, while the cell volume and plasma protein concentration fell, apparently a dilution effect. At the end of the diuresis, the plasma volume diminished in this case and the plasma protein concentration and cell volume rose at the same time. The patient lost a total of 17.2 kilograms of edema fluid during the course of his diuresis. His blood pressure decreased rapidly and remained about 140 systolic and 70 diastolic.

Clinically, there was some evidence that tonsillitis was the factor responsible for the renal lesion. However, in view of the presence of syphilis, cautious anti-syphilitic therapy was initiated including potassium iodide, several doses of bismuth and finally two doses of neoarsphenamine. The patient was improving until on May 12, 1935 he developed tonsillitis. On May 14, 1935 a peri-tonsillar abscess was incised with the liberation of considerable pus. The infection spread rapidly in spite of therapeutic measures and at the same time an acute exacerbation of his nephritis occurred with nitrogen retention. He was discharged against advice on May 12, 1935, his blood non-protein nitrogen having rapidly risen to 90 mg. per cent. He died at home the next day.

Case 3. M. W., aged 44, white male.

Admitted first on January 8, 1935. Three weeks prior to admission the patient had noted the insidious onset of swelling of the feet and rapid gain in weight. Two weeks before admission, he consulted his doctor who told him he had kidney trouble and placed him on a meat-free, salt-free diet. Edema became progressively worse and he was, therefore, referred to the hospital.

The patient states that he has always enjoyed good health. He has been a rather heavy drinker of corn liquor. There is no history of sore throats, upper respiratory infections or exposure to heavy metals. No history of hematuria.

Physical Examination: Blood pressure, 120 mm. of Hg systolic and 80 diastolic. A well developed large man weighing 118 kilograms. There is marked pretibial and presacral pitting edema. The heart and lungs are clear. The fundi oculi are normal.

Urine: Specific gravity 1.027, albumin 4 plus, no red blood cells. Numerous white blood cells, many small and medium coarse and fine granular casts. No red blood cells on repeated examinations.

Blood: Hemoglobin 15.8 gm. per 100 c.c. Red blood cells 5,030,000 per cu. mm. Non-protein nitrogen 31 mg. per cent. Total plasma proteins 3.78 gm. per 100 c.c. Plasma albumin 1.20 gm. per 100 c.c. Plasma globulin 2.58 gm. per 100 c.c. Cholesterol 500 mg. per 100 c.c. Wassermann and Kahn reactions negative.

Kidney function studies: Concentration test, maximum concentration 1.027 (corrected for albumin). Urea clearance, 104 per cent of normal (January 9).

Basal metabolic rate plus 3 per cent (January 12).

Therapy: He was placed on a high protein low salt diet. On January 11, and again on January 12, 14 and 16, 500 c.c. of 6 per cent acacia in normal saline were given intravenously. Diuresis occurred following the first injection of acacia and continued as shown in figure 3. At the patient's insistence, he was discharged on January 19, his edema having diminished considerably.

It is seen from figure 3 that following the acacia injection, a large increase in plasma volume occurred with an associated fall in cell volume and plasma protein concentration.

Readmission: Readmitted on April 10, 1935 with the complaint of recurrence of edema.

While adhering to the diet following discharge on January 19, 1935, the patient continued to lose edema and his weight reached a low point of 106.7 kilos. However, several weeks after discharge, he resumed his activities and ceased to follow

dietary instructions. Edema returned and he consulted several physicians who, after various therapeutic measures had been tried without success, referred him to the hospital for treatment.

Physical Examination: Blood pressure 120 mm. of Hg systolic and 70 diastolic. The patient is more edematous now than he has ever been. He weighs 126.25 kilos, and later events show that at least 36 kilos of this weight consist of edema fluid.

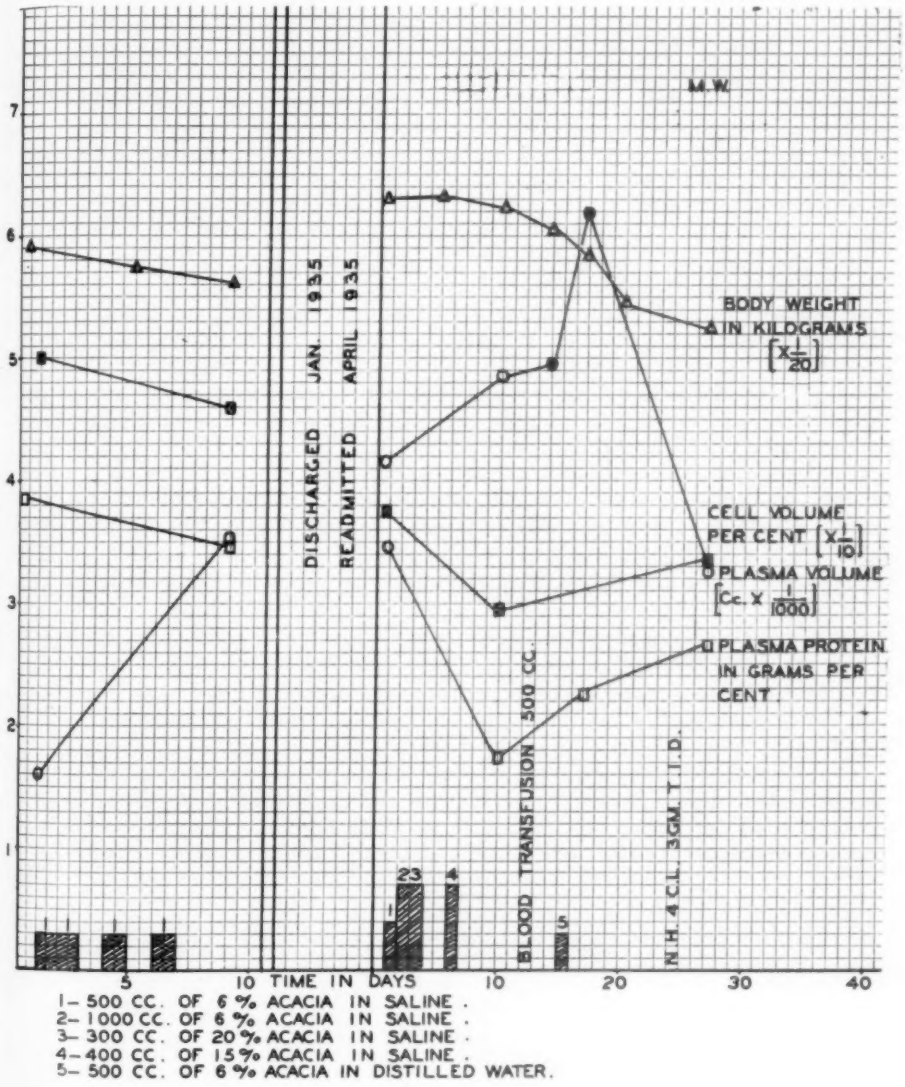
M.W.
BODY WEIGHT IN KILOGRAMS [X 1/20]
CELL VOLUME PER CENT [X 1/10]
PLASMA VOLUME [Cc. X 1/1000]
PLASMA PROTEIN IN GRAMS PER CENT.
DISCHARGED JAN. 1935
READMITTED APRIL 1935
BLOOD TRANSFUSION 500 CC.
N.H.4 CL. 3GM. T.I.D.
TIME IN DAYS
1- 500 CC. OF 6 % ACACIA IN SALINE.
2- 1000 CC. OF 6 % ACACIA IN SALINE.
3- 300 CC. OF 20 % ACACIA IN SALINE.
4- 400 CC. OF 15 % ACACIA IN SALINE.
5- 500 CC. OF 6 % ACACIA IN DISTILLED WATER.

FIG. 3.

The scrotum is tremendously distended, measuring 102 cm. in circumference. Ascites is present. There is no evidence of cardiac failure.

Urine: Specific gravity 1.020, albumin four plus. Microscopic, as before, no red blood cells.

Blood: Hemoglobin 14 grams per 100 c.c. Red blood cells, 4,400,000 per cu. mm. Non-protein nitrogen 35 mg. per cent. Total plasma protein 3.41 gm. per 100 c.c. Plasma albumin 0.71 gm. per 100 c.c. Plasma globulin 2.70 gm. per 100 c.c.

Kidney function studies: Urea clearance 97 per cent of normal (May 5).

Basal metabolic rate minus 25 per cent (May 10).

Therapy: The patient was placed on a high protein salt free diet. Acacia was given at the times and in the quantities and concentrations indicated in figure 3. On April 16, 0.5 c.c. of salyrgan was given intravenously. On April 22, salyrgan 1.0 c.c. was given intravenously. Between April 15 and 20, the patient also received a total of 37 gm. of potassium chloride by mouth. It is difficult in the face of the employment of several different diuretic agents to evaluate their respective rôles in the production of the moderate diuresis which occurred between April 10 and 24. On April 25, 500 c.c. of 6 per cent salt free acacia in distilled water were given intravenously. This injection was followed by a severe chill lasting 30 minutes and a temperature rise to 39.2° C. A period of oliguria lasting about 10 to 12 hours ensued. However, this was succeeded by a marked and rapid diuresis. The plasma volumes charted as of April 25 and April 27 are not actual measurements but are calculated on the basis of observed hemoglobin concentration changes. They indicate that following the injection of the last 30 gm. of acacia, a large rise in plasma volume occurred. Toward the end of the diuresis, the plasma volume returned to below the initial figure. By this time, the patient had lost 23 kilos, but still had edema. Ammonium chloride was started on May 5, 1935 and the patient gradually lost another 12 kilos of edema fluid. He was discharged almost edema free on June 6, 1935. His liver was not palpable during either admission.

Case 4. Z. R., white female, aged 22.

The patient was admitted on November 11, 1936 with the complaint of "kidney trouble." In January 1936 the patient noticed the insidious onset of edema of the ankles. Several days later she first complained of a severe sore throat. Her urine was found to contain large amounts of protein. Her family physician advised tonsillectomy which was performed on January 10. The patient remained in bed for one month during which time edema remained marked. She resumed her household activities in February 1936 and ate a normal diet. She continued to have edema of the legs and face which became more severe despite the employment of a wide variety of therapeutic measures. The patient was therefore referred to this hospital for treatment.

Physical Examination: Blood pressure 110 mm. of Hg systolic and 70 diastolic. The patient is a well developed young white woman. There is marked pitting edema of the subcutaneous tissues from the level of the tenth dorsal vertebra down. There is a small amount of pleural fluid in the right chest. A moderate amount of ascites is also present. The fundi oculi are normal. The heart is normal. The liver cannot be felt.

Urine: Amber, specific gravity 1.029, albumin three plus. Microscopic: Many hyaline casts, rare red blood cells, occasional white blood cell.

Blood: Hemoglobin 14.6 grams per 100 c.c. Red blood cells 5,380,000 per cu. mm. Non-protein nitrogen 40 mg. per cent. Total serum proteins 3.70 gm. per 100 c.c. Serum albumin 0.80 gm. per 100 c.c. Serum globulin 2.90 gm. per 100 c.c. Serum cholesterol 621 mg. per cent. Serum chlorides 554 mg. per cent. Blood Wassermann and Kahn reactions negative.

Kidney function tests: Urea clearance 67 per cent of normal (Dec. 4, 1936) and 77 per cent of normal (Dec. 22, 1936).

Basal metabolic rate minus 12 per cent (Dec. 2, 1936).

Therapy: The patient was placed in bed and given a diet low in salt and containing 60 gm. of protein per day. On December 10, 1936 the diet was changed to

120 gm. of protein and urea, 60 gm. per day by mouth, was given as a diuretic. Since no marked diuresis occurred on this regime, urea was discontinued on December 15, 1936 and acacia injections were started on December 17, 1936. As can be seen in figure 4, diuresis followed the second injection of 500 c.c. of 6 per cent acacia in normal saline. The patient lost a total of about 10 kilos of edema fluid in seven days and was practically edema free when discharged on December 24, 1936.

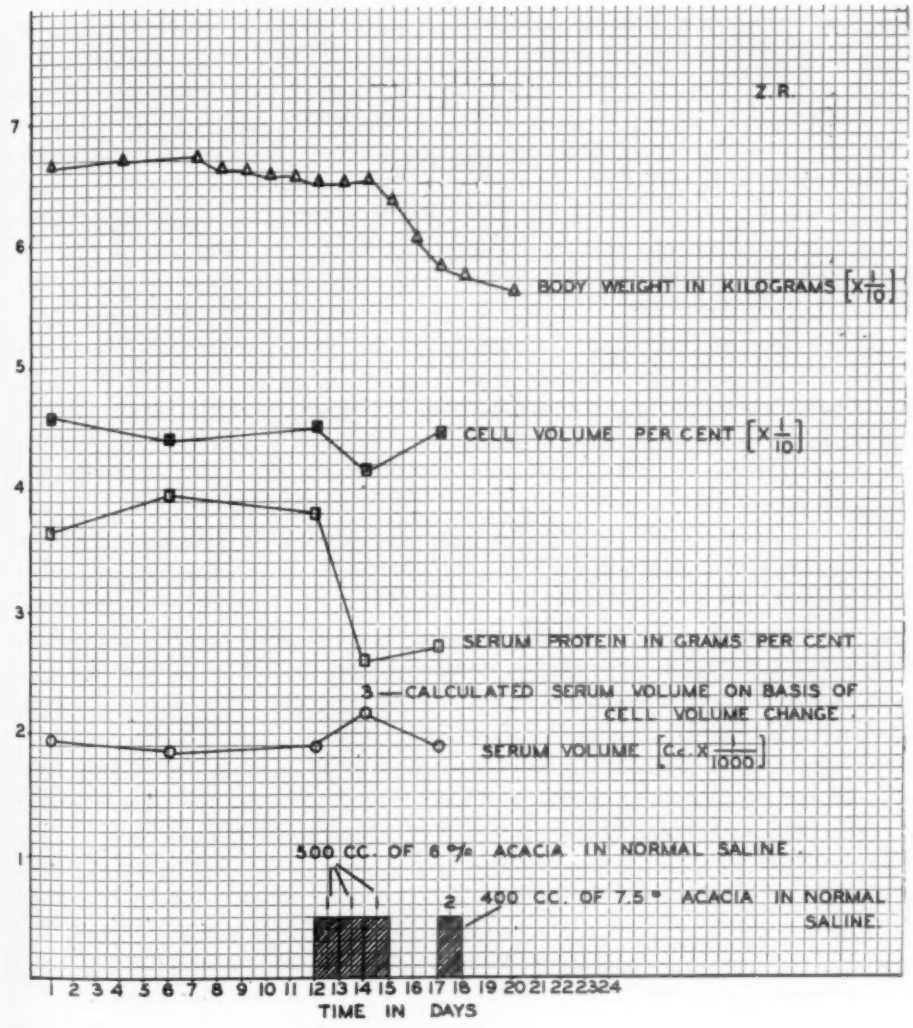
Z.R.
BODY WEIGHT IN KILOGRAMS [X 1/10]
CELL VOLUME PER CENT [X 1/10]
SERUM PROTEIN IN GRAMS PER CENT
3—CALCULATED SERUM VOLUME ON BASIS OF CELL VOLUME CHANGE.
SERUM VOLUME [C.C. X 1/1000]
500 CC. OF 6 % ACACIA IN NORMAL SALINE.
2 400 CC. OF 7.5 % ACACIA IN NORMAL SALINE.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TIME IN DAYS

FIG. 4.

DISCUSSION

Serum Volume Changes and Diuresis. When acacia in the concentration of 6 per cent or more is introduced into the blood stream of patients with hypoproteinemia, an immediate increase in plasma colloid osmotic pressure and in plasma volume must of necessity occur. However, the increase in

the plasma colloid osmotic pressure will cause fluid to be attracted to the blood stream and when a state of equilibrium is attained, it may well be that the increase in plasma volume will effectively counterbalance the original increase in plasma colloid osmotic pressure. The final result will, therefore, be an increase in the plasma volume and in the total circulating plasma colloid.

In the present report, the studies of plasma volume have been performed at times significantly distant from the acacia injections, since in this way the more permanent effects of acacia could be investigated. The striking feature of the results is that almost without exception, the persistence of diuresis following the injection of acacia was associated with increase in the plasma volume. In the absence of actual measurements of plasma colloid osmotic pressure, it is impossible to say whether it, too, increased during the periods of diuresis and hypervolemia. However, the decrease in plasma protein concentration noted during the same periods would indicate that if any rise in plasma colloid osmotic pressure did occur, it was probably of small magnitude. Since the most consistent change following acacia injection was the increase in plasma volume, it seems logical to suspect that this change was the one responsible for diuresis. This suggestion was originally advanced by Peters [8] in a stimulating discussion of the mechanism of acacia diuresis in nephrosis which concluded with the statement that " It may well be the fullness of the blood stream which provokes the diuretic response on the part of the kidneys."

The manner in which the " fullness of the blood stream " provokes diuresis is not apparent from the data at hand. It is, however, probable that the diuresis associated with increases in plasma volume is due to increased filtration of urine. This may be due to the opening of more glomeruli by the larger volume of blood or to an increase in the rate of blood flow through the kidneys. In the absence of actual measurements of these variables, the mechanism provoking diuresis must remain obscure.

If increase in plasma volume provokes diuresis in nephrotic states, some of the so-called " spontaneous " diureses which we occasionally see may thus be explained. When these diureses have occurred in the absence of any change in the plasma protein concentration, they have usually been classed as exceptions to the Starling theory. However, we now have evidence that large fluctuations in plasma volume and hence in the total circulating colloid may occur in nephrotic states without any changes in the plasma protein concentration.[9] During the " spontaneous " diureses, despite constant plasma protein concentrations, large rises in the total circulating colloid may have occurred. Such rises would act much like acacia in initiating and maintaining diuresis. Our data do not support the view that the absolute volume of the plasma at any given time is the factor responsible for diuresis. However, they do support the thesis that acutely induced increases in the plasma volume provoke diuresis. The cause for this is probably to be found in the fact that gradual changes in plasma volume are compensated for,

while the more acute changes exceed, for a time at least, the ability of the body to compensate.

Serum Protein Changes. Following the injection of acacia, in accord with the report of Dick and associates,[3] the plasma protein concentration decreased. This change was due in part to hemo-dilution. However, in three instances, hemo-dilution alone did not account for the decrease in plasma protein concentration. Measurements of the plasma volume in these patients revealed that the *total circulating plasma protein* (derived by multiplying the plasma volume by the plasma protein concentration), had actually decreased following the injection of acacia. It is not to be inferred that the regeneration of plasma protein was impaired, for in one carefully studied case,[10] regeneration of plasma protein remained active following the use of acacia. However, with diuresis, the urinary loss of protein increased sufficiently to account for the observed reduction in the total circulating plasma protein. The explanation for this increase in proteinuria is not evident but is now being sought in this clinic. At present, it is our belief that the increased proteinuria following acacia injection is due to increased glomerular filtration and not to a toxic action of acacia on the glomeruli. In accord with this belief are the data of Bing [11] who has suggested that changes in the degree of proteinuria in the same patient reflect changes in glomerular filtration.

Red Cell Volume Changes. The decrease in red cell volume following acacia therapy is largely a dilution effect.

Practical Considerations. It is apparent that in the cases here reported, diuresis was provoked by acacia in much smaller quantities than those used by others.[2, 3] Our studies indicate that the aim of acacia therapy is to increase the plasma volume, and this may be attained with relatively small dosage of acacia. We are now using intravenous injections of 500 c.c. of 6 per cent acacia in normal saline as a dose for average adults, and this is repeated at daily intervals for three or four days. If acacia is going to be effective, results should be apparent with this dosage in most cases. We see no point in forcing dosage much past this limit if no diuresis has resulted. If diuresis does occur, 30 gram doses may be repeated at intervals which will of necessity vary with individual cases. The plasma albumin level should be watched closely and if it falls too sharply, acacia therapy should be discontinued until the albumin level has been substantially improved.

In selecting cases for acacia therapy, the following suggestions may be of value. A previous adequate trial on a high protein salt-poor diet and diuretics such as urea or members of the saline diuretic group is definitely indicated in all cases. These therapeutic measures may well be supplemented with others aimed at increasing the plasma volume and plasma proteins, e.g., transfusions of whole blood, serum or plasma. If these measures fail, acacia therapy should be considered. Should an untoward reaction occur, the safest procedure is to stop using acacia. The use of acacia need not be

limited to cases of so-called nephrosis, for our results have been equally good in cases of chronic active glomerulonephritis in the nephrotic stage.

Conclusions

1. Acacia provokes diuresis in nephrotic edema by increasing the plasma volume.

2. A method of administration of acacia is presented, based upon the above concept of its mode of action, and involving the use of relatively small doses.

3. The so-called deleterious effects of acacia described by other writers have been explained on grounds other than those of toxicity of acacia.

4. Acacia has a definite place in the therapy of properly selected cases of nephrotic edema.

I am deeply indebted to Dr. John P. Peters for his valuable advice.

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RECENT STUDIES ON THE EXCRETION OF MALE SEX HORMONES IN MAN *

By F. C. Koch, *Chicago, Illinois*

Although androsterone and dehydroandrosterone, two substances of androgenic character, have been separated from human urine, very little is known as to the significance of their occurrence and still less as to the fluctuations in the rate of excretion in health and disease. It is generally assumed that these substances are waste products formed from testosterone secreted into the blood stream by the gonads, but it is just as reasonable to expect that one or both of these urinary products may be precursors of testosterone or that they, or still other androgenic substances, may originate in part in other tissues or be present in our food.

A survey of the literature [1] reveals that too many investigators have attempted to answer some of these questions by extraction and biological assay methods which are practically worthless for quantitative purposes. In this paper I propose to present a summary of some of the results which my colleagues and I have published on this problem in more detail elsewhere.[1, 2, 3]

By means of the comb-growth response in the capon [4] and a complete extraction procedure for urine,[5] we arrive at values which are distinctly higher than the highest reported elsewhere and 20 to 60 times the lowest reported by others.[6, 7] Our higher values are due to two factors—the complete extraction of the urine, the liberation of androgenic activity by acid hydrolysis from what appears to be a conjugated form, and the prevention of the subsequent destruction thereof by acid by limiting the hydrolysis to the time of maximum yield.[3] Table 1 clearly shows that 15 minutes' acid-hydrolysis leads to a 70 to 160 per cent increase in androgenic units, but that two hours' boiling again leads to a loss of activity. The nature of the con-

Table I

The Effect of Length of Time of Acid Hydrolysis in Three Urines on the Yield of Androgens

Sample	International androgenic units per liter obtained when boiled for:					
	0 min.	¼ hr.	1 hr.	2 hrs.	6 hrs.	12 hrs.
A	20	53	37	29	20	—
B	31	50	—	35	—	25
C	27	66	54	38	33	—

* Presented at the St. Louis meeting of the American College of Physicians, April 19, 1937.

From the Department of Biochemistry, The University of Chicago.

jugated form, of the destructive process, and the significance of the conjugation, remain to be determined.

Our studies on normal men and women covered urine collections for 27 to 45 consecutive days. The collections from men usually were pooled for three consecutive days. From the women we received two-day samples except during menstruation, when the excretions were pooled for the period. These urines were completely extracted, the androgenic and estrogenic activities separated from each other and assayed on capons and spayed rats respectively.

The results are given in tables 2, 3, and 4. In seven of the eight subjects we hydrolyzed the urine for two hours because at the time we had not discovered the importance of a brief period of hydrolysis. In subject 4, we limited the hydrolysis to 15 minutes, hence the greater yield of androgenic units in this individual. In both men and women we observe marked daily fluctuations in the urinary excretion of androgens and estrogens. The rates of excretion of the two activities bear no relation to each other.

Only one of the normal men gave an indication of a cycle in the rate of excretion of androgenic substances. Although the daily variations for a given individual and for the group of men are marked, the daily averages for the four individuals are remarkably constant, ranging from 63 to 68 international androgenic units. The averages for the estrogenic activity are also remarkably close, that is, 9 to 12 gamma theelin per day. By dividing the androgenic units per day by the gamma of theelin per day, we obtain

TABLE II

The Daily Urinary Excretion of Androgenic and Estrogenic Activities by Four Normal Men
"An" designates international androgenic units per day.
"Es" designates estrogenic activity as gamma of theelin per day.

Subject 1 age 27 yrs.				Subject 2 age 26 yrs.				Subject 3 age 30 yrs.				Subject 4 age 35 yrs.			
Days	An	Es	An/Es	Days	An	Es	An/Es	Days	An	Es	An/Es	Days	An	Es	An/Es
3	25	10	3	3	40	5	8	3	30	12	3	2	25	8	3
"	39	8	5	"	28	10	3	"	37	10	4	3	69	16	4
"	50	4	12	"	27	2	14	"	45	10	5	"	25	5	5
"	34	10	3	"	37	18	2	"	52	26	2	"	38	13	3
"	38	8	5	"	32	2	16	"	42	10	4	"	23	16	2
"	24	8	3	"	65	3	22	"	24	4	6	"	58	11	5
"	33	5	7	"	20	2	10	"	79	14	6	"	65	11	6
"	37	5	8	"	41	20	2	"	49	10	5	"	42	10	4
"	45	10	5	"	53	3	18	4	41	11	4	"	41	16	3
"	48	5	10	"	36	2	18	"	36	2	18	"	31	10	3
"	63	18	4	"	52	18	3	3	44	2	22	4	30	21	2
"	38	10	4	"	lost			"	40	29	1	3	34	10	3
"	34	10	3	"	46	18	3	"	lost						
"	29	9	3	"	62	8	8	"	13	14	1				
Ave. values	38	9	4.2		41	9	4.6		41	10	4.1		40	12	3.3

The urine of these subjects was boiled two hours before extraction.

TABLE III

The Daily Urinary Excretion of Androgenic and Estrogenic Activities by Four Normal Women
"An" designates international androgenic units per day.
"Es" designates estrogenic activity as gamma of theelin per day.

Subject 1 age 34 yrs.				Subject 2 age 31 yrs.				Subject 3 age 24 yrs.				Subject 4* age 23 yrs.			
Days	An	Es	An/Es	Days	An	Es	An/Es	Days	An	Es	An/Es	Days	An	Es	An/Es
5 M	22	7	3	3	20	44	0.5	2 M	22	5	4	2	70	21	3
2	42	31	1	2	35	38	0.9	2 M	13	5	3	5 M	45	4	11
"	21	25	0.8	"	30	22	1	"	28	10	0.4	2	45	8	6
"	31	28	1	"	18	53	0.3	"	36	21	2	"	45	8	6
"	29	18	2	"	27	30	0.9	"	19	9	2	"	42	11	4
"	23	21	1	"	27	30	0.9	"	22	25	0.9	"	49	28	2
"	19	40	0.5	"	26	60	0.4	"	42	21	2	"	lost		
"	20	35	0.6	"	28	40	0.7	"	16	16	1	"	50	25	2
"	22	30	0.7	"	25	40	0.6	"	46	22	2	"	53	16	3
"	17	34	0.5	"	26	40	0.7	"	lost			"	60	16	4
"	lost			"	18	18	1	"	23	27	0.9	"	63	41	2
"	25	30	0.8	7 M	26	13	2	"	36	18	2	"	56	32	2
								"	29	28	1	"	85	28	3
								"	20	10	2	"	68	24	3
								"	24	22	1				
Ave. values	25	27	0.93		26	36	0.72		28	18	1.6		56	20	2.8*

* The urine of subject 4 was hydrolyzed for 15 minutes, the others for 2 hours.
M = menses.

TABLE IV

A Summary of the Average Values from Tables II and III
"An^{15}" designates the international androgenic units per day by the 15-minute boiling-procedure.
"An^{120}" the same by the 2-hour boiling-procedure.
"Es" designates the estrogenic activity as gamma of theelin per day.

Men						Women					
Subject	An^{15}	An^{120}	Es	An^{15}/Es	An^{120}/Es	Subject	An^{15}	An^{120}	Es	An^{15}/Es	An^{120}/Es
1	63*	38	9	7.0	4.2	1	42*	25	27	1.6	0.93
2	68*	41	9	7.6	4.6	2	43*	26	36	1.2	0.72
3	68*	41	10	6.8	4.1	3	47*	28	18	2.5	1.5
4	66*	40	12	5.5	3.3	4	56	34*	20	2.8	1.7
Average				6.9	4.1					2.0	1.2

* These values are calculated on the assumption that the yield of androgenic activity is increased by 66 per cent over the 2-hour hydrolysis if boiled 15 minutes instead.

what we call our An/Es ratios. This ratio ranges from 1 to 22 for the men, but when averaged again covers a relatively narrow range of 5.5 to 7.6.

In the normal women the rate of excretion of androgens is also variable and of a high order, but distinctly lower than in men. The averages are again relatively constant as shown in table 4. The daily excretion of estrogens also varies considerably in normal women, but tends to be higher than in men. There is good evidence of the periodic rise and fall in the excre-

tion of estrogens in relation to the menses. The excretion of the estrogens generally is higher 7 to 14 days after the onset of menstruation and again 6 to 12 days before the next period. The excretion is lowest during menstruation. The An/Es ratios also vary tremendously in each of the four women, ranging from 0.3 to 11, but the averages range from 1.2 to 2.8 for women as compared with 5.5 to 7.6 for men (table 4). This change in ratio is due to the fall in excretion of androgens and rise in estrogens in women as compared with men.

In the present state of our knowledge we do not know how to explain these remarkable fluctuations. It is very probable that the exogenous source of these hormones is negligible because their presence in foods is limited to exceedingly small amounts and because their absorption probably is relatively difficult. Whether the endogenous source is limited to the gonads or whether the suprarenals and liver are also involved in the healthy individual, remains to be determined.

Studies in Hypogonadism. In two castrates we found 1 to 3.5 international capon units of androgens and 3 to 4.5 gamma theelin per liter of urine. These amounts may easily be of exogenous origin. In seven eunuchoids, the daily excretion varied from 5 to 19 international capon units of androgens and 1 to 9 gamma theelin per day. In two cryptorchids, the values were 9 to 31 and 1 to 6, respectively. Apparently there is no doubt that these extreme conditions lead to a very low excretion of both sex hormones. However, in spite of the low absolute excretion, the An/Es ratios ranged from 0.3 to 31.

Studies in Gynecomastia. In three cases of gynecomastia we found 0 to 37 androgenic units and 5 to 15 gamma theelin excreted per day. The An/Es ratios ranged from 0.1 to 2.5, but no excess excretion of estrogens was observed.

Studies in Virilism. In thirteen cases of virilism without obvious adrenal involvement, the daily excretion of androgens ranged from 5 to 55; of estrogens, from 4 to 19, resulting in ratios ranging from 0.2 to 7.5. In four cases with adrenal involvement, the androgen excretion values were 0, 44, 69, and 480 international units per day, and 4 to 8 gamma estrogens per day. The case with the highest value gave the An/Es ratio of 60. In general there appears to be a tendency to an increased An/Es ratio with a fall in excretion of estrogens in cases of virilism. This is, however, not always true. The patient with an excretion of 480 international androgenic units is of special interest for several reasons. First, because after removal of the adrenal cancer, the hirsutism disappeared; second, because absorption spectra studies indicate a possibly closer chemical relation of the androgenic substance to testosterone than to androsterone or dehydroandrosterone; and third, because studies by others on an oxidation product of a cortical adrenal hormone demonstrate its relation to testosterone chemically as well as biologically.[8, 9] This oxidation product was found to be one-sixth to one-

fourth as active as androsterone in the capon. Others [10, 11] have found exceedingly high concentrations of androgens in the urine from cases of adrenal tumors.

Summary

1. There are marked daily fluctuations in the urinary excretion of androgens and estrogens in normal men and women.

2. The average daily excretion of androgens is 63 to 68 international units in men and 42 to 56 units in women.

3. The average daily excretion of estrogens, calculated as gamma of theelin, is 9 to 12 gamma for men and 18 to 36 gamma for women.

4. In male castrates, exceedingly small amounts of sex hormones are found in the urine.

5. In eunuchoids the excretions of sex hormones are distinctly lower than in normal individuals.

6. In gynecomastia, no excess excretion of estrogens was observed.

7. In virilism there is a tendency toward a lower excretion of estrogens with a normal or higher excretion of androgens.

8. In some cases of virilism with adrenal involvement, the excretion of androgens is exceedingly high.

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MYXEDEMA; PRESENTATION OF A GROUP OF CASES ILLUSTRATING PHASES OF THE DISEASE WHICH ARE RECEIVING ATTENTION IN RECENT LITERATURE *

By A. RAVIN, M.D., *Denver, Colorado*

RECENT investigations of myxedema have greatly increased our knowledge of the disease. Attention has been directed to newly recognized symptoms, to changes in the cholesterol and carbohydrate metabolism, and especially to the heart findings. The following case histories are presented because they illustrate these and other features of the disease. Since the cardiovascular changes in myxedema have been the object of so much discussion, they have been stressed in this article. A hypothesis to explain these changes on a pathological physiological basis is presented.

CASE REPORTS

Case 1. *Spontaneous myxedema in a woman aged 51; typical signs and symptoms; chronic valvular disease of heart in association with "myxedema heart"; markedly dilated heart decreasing in size with thyroid therapy; increase in voltage in electrocardiogram with treatment; small maintenance dose of thyroid.*

B. G., a white woman of 51, entered the clinic in January 1934 complaining of "shortness of breath," "lack of life," and "difficulty in hearing." One sister had diabetes and her father had had a cancer of the eyelid. Menopause occurred eight years ago. Her knees were stiff and swollen at 19 years of age. Patient believed that she was quite well until six or seven years ago. At that time she noticed that her eyelids became puffy; shortly afterwards her feet became edematous and recently her entire body, especially her abdomen, had begun to swell. She lacked energy. Memory was poor and she could neither think nor act rapidly. Her hearing had become poor and her voice husky in recent years. She could not stand cold weather. Her hands did not perspire. The skin had become dry and scaly. In spite of a poor appetite, weight had not been lost.

Examination revealed a small white woman who walked with a slow shuffling gait. She reacted slowly and talked slowly in a rather coarse, low-pitched voice. The skin was pale, dry, coarse and scaly. On each cheek was a small area of cyanosis. Hair was present only on the eyebrows, scalp, and pubis and in these regions it was scant, coarse, and brittle. The facial expression was dull and heavy. The cheeks were puffy and the lips thick. The thyroid could not be palpated. A few fine râles were heard at the bases of both lungs posteriorly. The blood pressure was 138 systolic and 102 diastolic. The pulse rate was 60 per minute with a regular rhythm. The heart was enlarged to percussion. A systolic murmur, most intense at the apex, was heard over the entire precordium. There was very little evidence of peripheral arteriosclerosis. The abdomen was distended but no shifting dullness was obtained. The liver was not palpated and was not down to percussion. A pitting edema of both legs was present.

The basal metabolic rate was minus 31, the blood cholesterol 300 mg. per 100 c.c.,

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From the Department of Medicine, University of Colorado School of Medicine.

the urine normal and the blood Wassermann test negative. The blood contained 3,470,000 red blood cells per cu. mm. and 9.8 grams of hemoglobin per 100 c.c. The gastric analysis (test meal) showed no free hydrochloric acid and a total acidity of 8 degrees. The sugar tolerance curve (1.75 grams of glucose per kilogram body weight was given in all sugar tolerance tests) showed a somewhat diminished tolerance; the peak was at 192 in the first hour with a return to normal at three hours. All complexes in all leads of the electrocardiogram were of low voltage. Left axis deviation was present. The chest roentgen-ray (figure 1, A) revealed a bilaterally enlarged heart.

One-half grain of desiccated thyroid (Lilly's) was found to be sufficient to keep the basal metabolic rate within normal limits. Marked clinical improvement was evident shortly after starting treatment. The patient began to react more rapidly, walk more rapidly, and speak more rapidly. The puffiness gradually left her cheeks and eyes and the dull, myxedematous facies gave way to a more alert expression. The skin became more smooth and oily and hair began to grow more abundantly. Fatigue and weakness diminished. The edema of the extremities left. As the heart action became more vigorous, the systolic murmur remained and increased somewhat in intensity. This finding, combined with a history of "rheumatism" at the age of 19, made the diagnosis of rheumatic heart disease with mitral insufficiency very probable.

The remarkable changes which occurred in the size of the heart are illustrated in figure 1. On 4/12/34, the date of the last film, the basal metabolic rate was plus eight, the pulse rate 62 per minute, the blood pressure 135 systolic and 90 diastolic, the hemoglobin 12.8 grams per 100 c.c. and the red blood cell count 5,100,000 per cu. mm. The electrocardiogram showed an increase in voltage of all complexes in all leads; the left axis deviation persisted. A gastric analysis still showed an achlorhydria with a total acidity of 10 degrees. A sugar tolerance on 5/27/34 revealed a peak of 220 in one hour with a return to normal in three hours.

Note: (1) The very small dose of desiccated thyroid required to keep the basal metabolic rate at normal and produce the changes noted. (2) The remarkable decrease in heart size under thyroid therapy. (3) The low voltage in the electrocardiogram associated with the enlarged heart and the increase in voltage as the heart diminished in size under thyroid therapy. (4) The association of "myxedema heart" with a valvular lesion probably of rheumatic origin. (5) The family history of diabetes in a sister and the presence of a somewhat decreased sugar tolerance in the myxedematous state with a further decrease in tolerance after treatment.

Case 2. *Spontaneous myxedema in a woman aged 31; typical signs and symptoms, including menorrhagia; variations in heart size with degree of hypothyroidism; association of rheumatic heart lesions and "myxedema heart."*

M. S., a white woman, aged 31, entered the clinic on 3/24/31 complaining of extreme dyspnea on exertion and menorrhagia. About two years previous to her entrance she began to notice difficulty in breathing on exertion. She suffered constantly from extreme lassitude. In the last few years, although her appetite had remained the same, she had gained 30 pounds in weight. She complained also of frequent headaches, occasional numbness of the right forearm and hand, painful and excessive menses, and sterility. The family history was essentially negative. Her husband had tuberculosis. There was no history of rheumatic fever, chorea, or frequent sore throats. Physical examination on admission showed an obese woman with puffy face and swollen eyelids, dry and scaly skin, and coarse hair. Blood

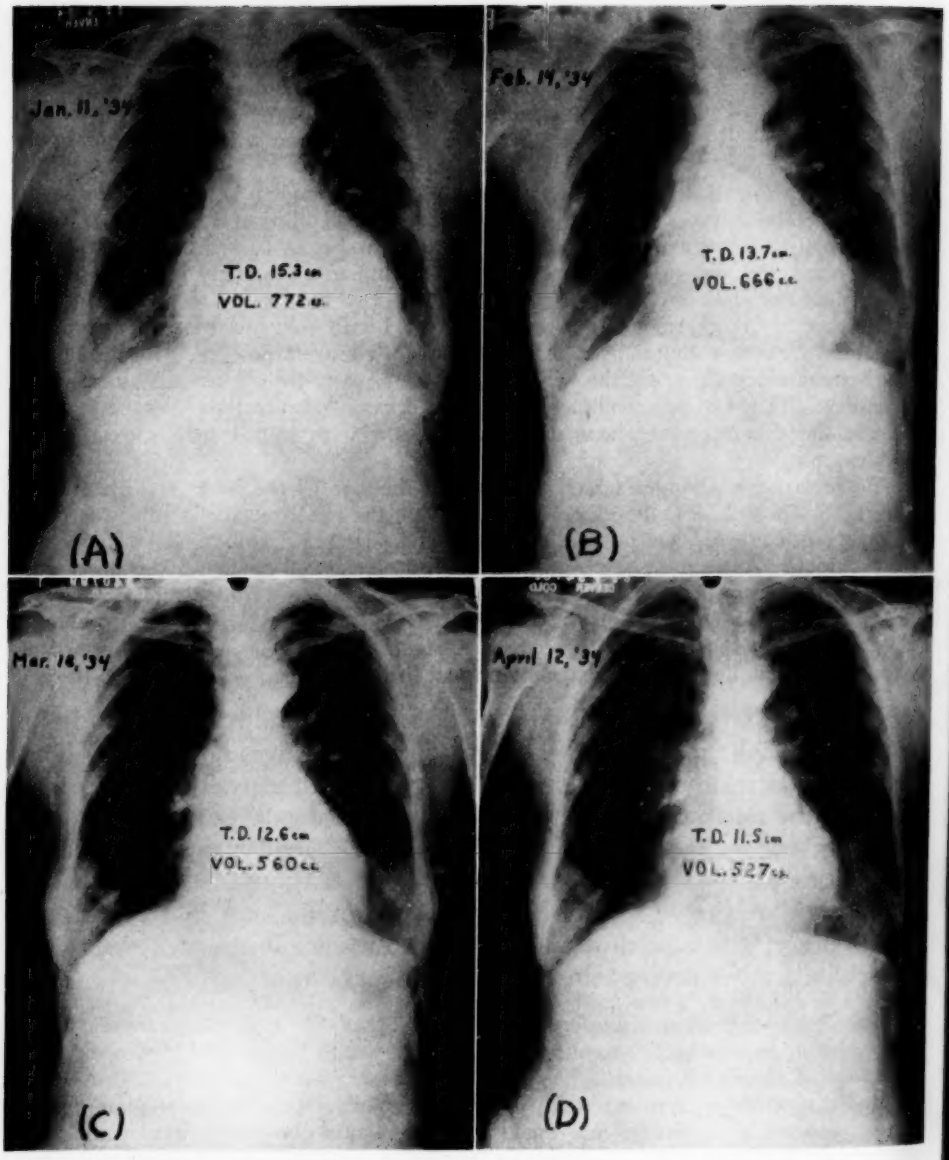

FIG. 1. Case 1. (*A*) Before treatment. BMR —31. Blood cholesterol 300 mg. per 100 c.c.
(*B*) One month after starting treatment. BMR plus 3. Blood cholesterol 180 mg. per 100 c.c.
(*C*) Two months after starting treatment. BMR plus 1.
(*D*) Three months after starting treatment. BMR plus 8.

pressure was 120 systolic and 80 diastolic. Pulse rate 62. No murmurs were heard. The basal metabolic rate was minus 30.

Under thyroid therapy the patient improved marvelously. In August 1932, however, she stopped coming to the clinic. She continued to take thyroid for a number of months and then stopped. In August 1934 she returned with very much the same story as on her first admission. She felt weak, tired easily and had no

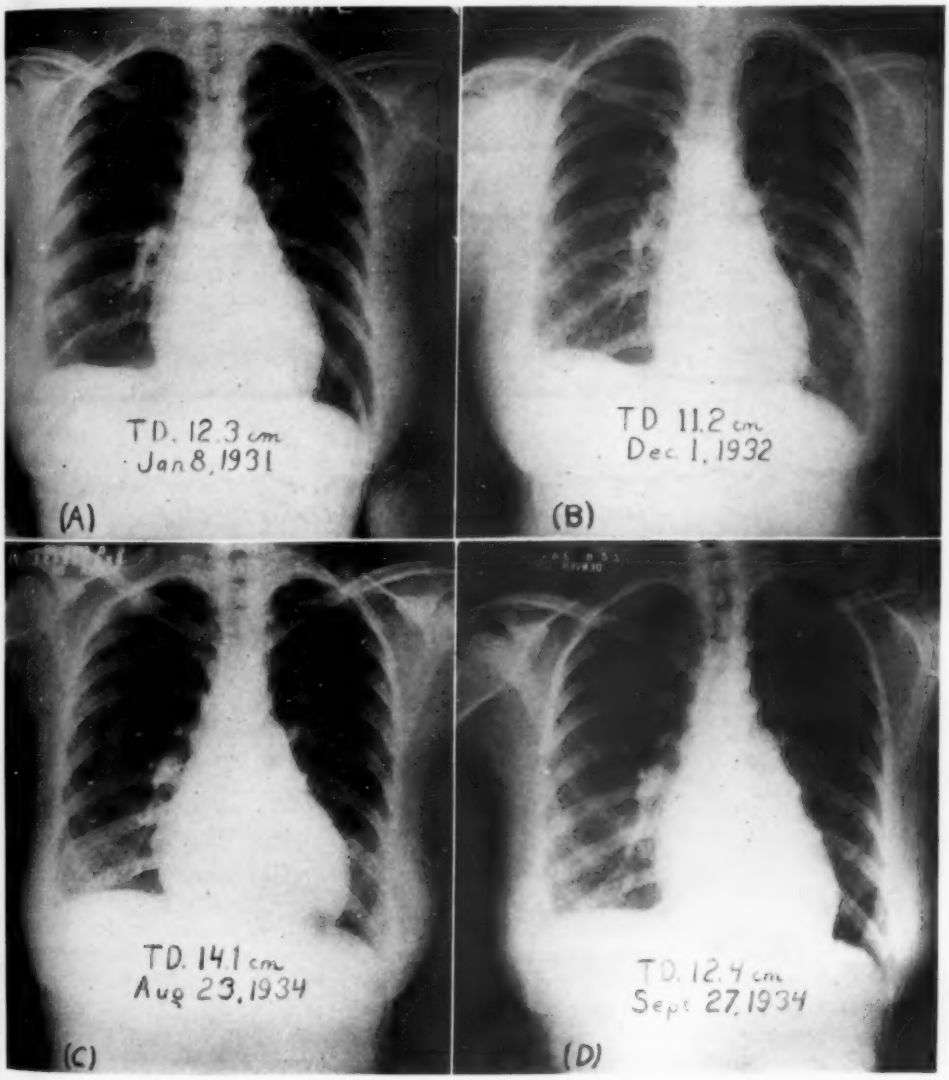

FIG. 2. Case 2. (*A*) Two months before patient's first entrance into clinic. BMR at time of admission into clinic was —30.

(*B*) Patient had been taking thyroid for over one and a half years. BMR —10. It must be noted in comparing the plates that although in the other three plates the diaphragm is almost at identical levels, in this plate it is slightly lower.

(*C*) Patient had been without thyroid for about one and a half years. BMR —36.

(*D*) After about four weeks of thyroid therapy. BMR —14.

energy. Her entire body seemed, to her, to be more or less swollen. Her skin had recently become coarse and her finger nails brittle. Examination revealed most of the signs of myxedema: slow response; dry, coarse skin; puffy cheeks and swollen eyelids. The heart was enlarged to percussion. No murmurs were heard. The basal metabolic rate was minus 34 and blood cholesterol 236 mg. per 100 c.c. The sugar tolerance curve was normal. Electrocardiogram revealed a low voltage of all complexes.

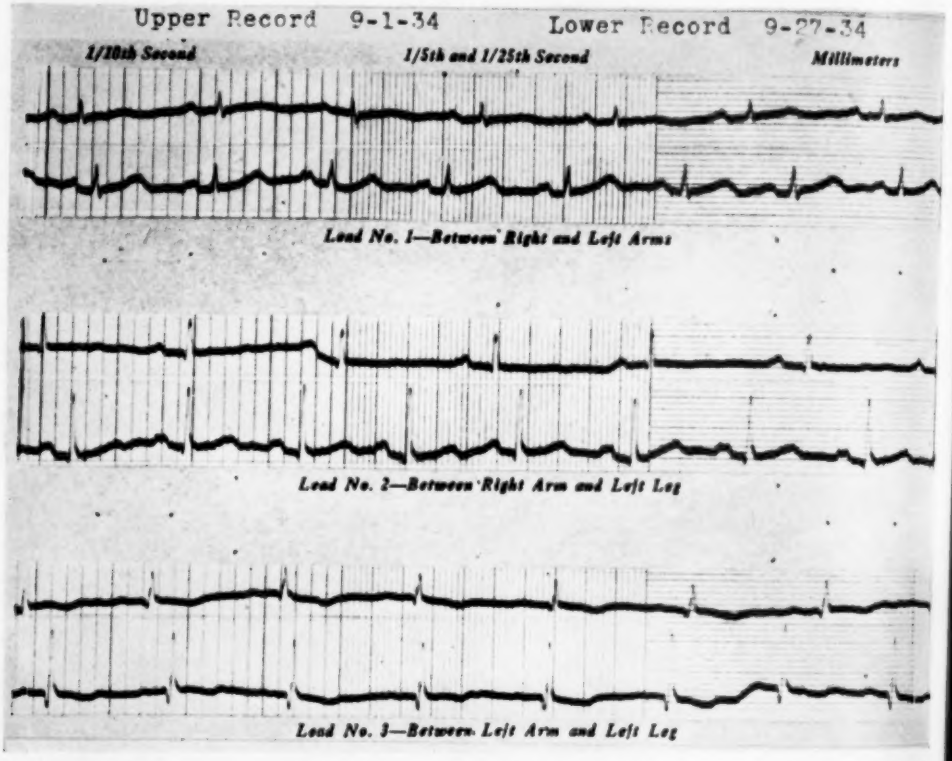
Upper Record 9-1-34
Lower Record 9-27-34
1/10th Second
1/5th and 1/25th Second
Millimeters
Lead No. 1—Between Right and Left Arms
Lead No. 2—Between Right Arm and Left Leg
Lead No. 3—Between Left Arm and Left Leg

FIG. 3. Electrocardiographs taken on Case 2. Upper tracing on 9–1–34 before thyroid therapy. Lower tracing on 9–27–34 after about four weeks of treatment.

Four weeks after starting thyroid therapy (final maintenance dose was three grains of desiccated thyroid daily) the patient showed the usual signs of improvement. Examination of the heart at this time showed it to be normal in size. Very definite mid-diastolic, presystolic, and systolic murmurs were heard and the diagnosis of mitral stenosis and insufficiency was beyond question. These murmurs were not heard before treatment in spite of several careful examinations. The interesting changes which occurred in the size of the heart are illustrated in figure 2. The electrocardiogram showed increased voltage throughout (figure 3). A sugar tolerance taken eight months after starting treatment was normal. A blood cholesterol at the same time was 137 mg. per 100 c.c.

Note: (1) Variations in heart size corresponding to degree of hypothyroidism. (2) Association of "myxedema heart" and rheumatic heart lesions. (3) Menorrhagia, which is referred to as of frequent occurrence

in myxedema. (4) Absence of the characteristic murmurs of mitral stenosis and insufficiency in the hypothyroid state. Several factors are probably involved. Most important is probably the decrease in velocity of blood flow. The diastolic murmurs of mitral stenosis will sometimes disappear when auricular fibrillation sets in, and the explanation usually given is that the absence of murmurs results from the decrease in velocity of blood flow. The conditions appear analogous. The increased viscosity of the blood in myxedema may hinder the production of murmurs. The possibility of dilated rings in a dilated heart must be considered.

Case 3. *Spontaneous myxedema in a 16 year old girl; typical signs and symptoms; heart size within normal limits before treatment with decrease in size after treatment; abnormal electrocardiographic features with change to normal after thyroid therapy.*

S. C., a white girl, aged 16, entered the clinic on 1/15/34 with a history of being tired and cold all the time, having no appetite, swelling of the feet, and infrequent menses. Symptoms had been present for the last five years and during that time she had been told by a private physician that she had heart and kidney trouble and had been in a hospital with a diagnosis of cardio-renal disease. Physical examination revealed enough of the signs of myxedema to make the diagnosis quite evident—mental retardation, pale, dry skin, dull facies, marked supraclavicular pads of fat (figure 4) and slow pulse. The heart was apparently normal in size with a transverse diameter of 10.3 cm. There was no edema of the extremities. The basal metabolic rate was minus 41; blood cholesterol 350 mg. per 100 c.c.; fasting blood sugar was 64 mg. per 100 c.c. The electrocardiogram revealed flat T-waves in all leads, right axis deviation, and a QRS spread of 0.12 second. The patient showed the usual

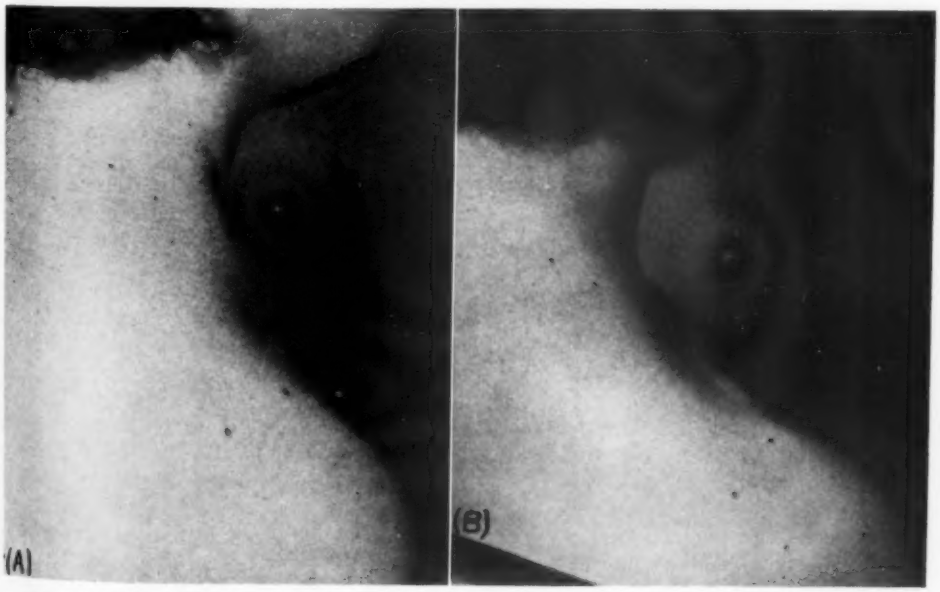

FIG. 4. Case 3. (*A*) Taken on 1–12–34 before starting thyroid therapy. (*B*) Taken on 5–28–34 after about five months of treatment. Note loss of the supraclavicular pad of fat.

marked and gratifying improvement with thyroid. The transverse diameter of the heart decreased to 9.6 cm. The electrocardiogram now showed T-waves of good voltage in all leads, normal axis deviation, and a QRS spread of 0.08 second.

Note: (1) Change in heart size even though the heart was apparently normal in size before treatment. (2) Marked electrocardiographic changes with a heart of apparently normal size. (3) The erroneous diagnosis of renal, or cardio-renal disease, not infrequently made in these cases.

Case 4. *Postoperative myxedema in a woman aged 27; mental reactivity out of proportion to myxedematous state; abnormal electrocardiograph with heart of normal size; marked anemia responding only to iron administration; prolonged tendon reflexes.*

J. B., a white woman, aged 27, entered the clinic on 11/27/34 complaining of "nervousness and palpitation" of several years' duration. In 1928 she noticed some enlargement of her neck; her nervousness and palpitation began about the same time. The next year exophthalmus, more prominent on the left, appeared. In July 1933 the diagnosis of toxic goiter was made and a thyroidectomy performed. This resulted in a temporary improvement of the symptoms but the nervousness and palpitation soon returned. On entrance into the clinic she complained also of being very weak and tiring easily. Although her appetite was poor, it was significant that she had not been losing weight. For several months a puffiness of the face and eyes had been noticed. She was sensitive to cold and her skin had become dry and coarse. Menstruation had begun at 14 and had been regular and normal until the toxic goiter developed, when the flow became excessive; after thyroidectomy, the flow became normal.

Patient was very talkative and spoke rather rapidly. She thought and responded with normal or increased rapidity. In general, her behavior corresponded more with that of a hyperthyroid than a hypothyroid individual. The facies presented a peculiar combination of the residue of hyperthyroidism (exophthalmus) and the features of hypothyroidism (puffy cheeks and eyelids, pasty skin). The skin was pale, dry and scaly. The blood pressure was 100 systolic and 76 diastolic. Pulse rate was 70 per minute and regular. Heart sounds were faint. There was no evidence of peripheral edema. Reflexes showed the prolonged contraction considered by Chaney[12] as pathognomonic of myxedema.

The basal metabolic rate was minus 30; the blood cholesterol 310 mg. per 100 c.c.; the urine normal; and the blood Wassermann test negative. The blood contained 3,270,000 red blood cells per cu. mm. and 8.8 grams of hemoglobin per 100 c.c. The sugar tolerance curve was normal, possibly slightly high, as the peak was at 176. Roentgen-ray showed the heart to be of normal size and appearance. The electrocardiogram revealed a low voltage of all complexes in all leads; the T-wave in Lead II was iso-electric.

Desiccated thyroid, one-half grain daily, was started and the dose was gradually increased to two grains daily. On this dose the basal metabolic rate became and remained normal (minus 7 to plus 9) and the blood cholesterol fell to 173 mg. per 100 c.c. The heart showed no significant change in size. The voltage of the T-wave in Lead II became one mm. and the voltage of the other complexes increased slightly. The change in the patient's condition was the remarkable one usually seen in these cases; she felt well and had very few complaints. On 4/4/35, five months after starting thyroid therapy, the hemoglobin was still 8.8 grams per 100 c.c. in spite of the improvement in the other signs and symptoms. Iron by mouth was started and on 6/7/35 the hemoglobin had increased to 13.7 grams per 100 c.c. Figure 5 shows the change in the Achilles tendon reflex which occurred under treatment.

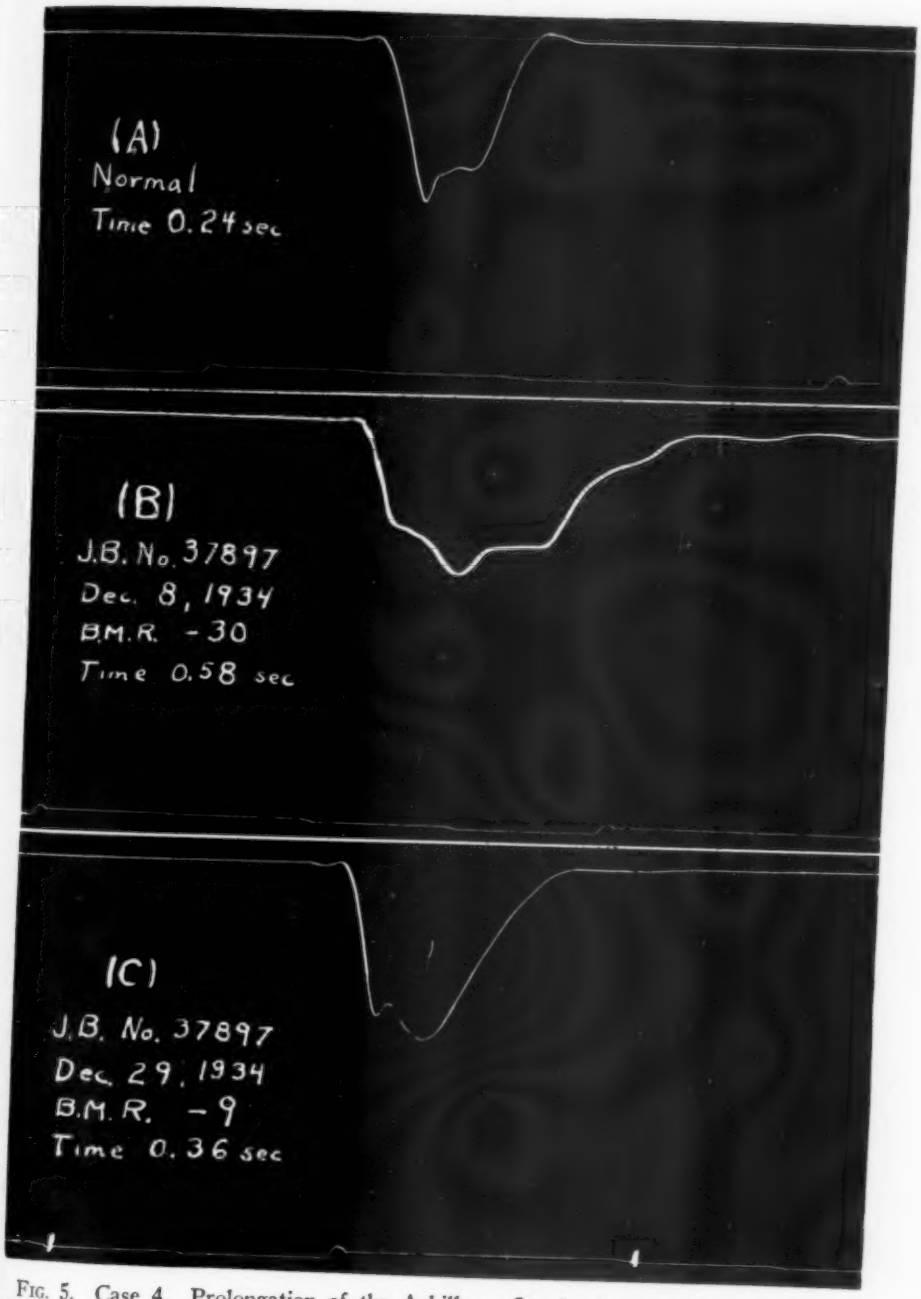

FIG. 5. Case 4. Prolongation of the Achilles reflex in the myxedematous state (*B*) and shortening after thyroid therapy (*C*). A normal record (*A*) is presented for comparison.

Note: (1) The presence of a mental activity such as one might expect in hyperthyroidism persisting after the physical and laboratory signs of myxedema had developed. It is, of course, probable that the patient was mentally retarded in comparison to her previous hyperthyroid state; she still showed, however, a mental reactivity out of all proportion to her hypothyroid state. (2) The presence of low voltage in the electrocardiogram with a heart of normal size. (3) The most notable change in the electrocardiogram after therapy was increase in the voltage of the T-wave in Lead II. (4) The failure of the rather marked anemia to respond to thyroid therapy and the good response when iron was given. (5) The presence of the prolonged reflex as noted especially in the Achilles tendon reflex.

Case 5. *Spontaneous myxedema in a woman, aged 51, with an interesting family history of diabetes.*

M. M., a white woman, aged 51, entered the clinic on 12/18/34 with numerous complaints, including the usual ones of fatigue, shortness of breath, inability to tolerate cold, poor appetite, constipation and slow mentation. Examination revealed the common signs of myxedema. The basal metabolic rate was minus 38; the blood cholesterol 283 mg. per 100 c.c.; the blood Wassermann test negative. Urine was normal except for a small number of pus cells. The blood count showed 3,800,000 red blood cells per cu. mm. and 12.5 grams of hemoglobin per 100 c.c. The sugar tolerance curve was normal. The gastric test meal showed no free hydrochloric acid and a total acidity of eight degrees. Roentgen-ray revealed a normal sized heart. In the electrocardiogram inverted T-waves in all leads, low voltage, and a slight left axis deviation were present.

Three grains of desiccated thyroid daily were required to keep the basal metabolic rate within normal limits. Laboratory tests six months after starting treatment were as follows: Red blood count 4,250,000 cells per cu. mm.; hemoglobin 14.5 grams per 100 c.c., blood cholesterol 167 mg. per 100 c.c.; sugar tolerance normal—the curve was somewhat flatter than before treatment; gastric test meal unchanged. Heart size was unchanged. The electrocardiogram had become normal with an increase in voltage of the QRS complexes, upright T-waves in all leads, and no axis deviation.

Of special interest in this case is the family history. A sister died of diabetes. A son died in diabetic coma. A daughter has diabetes and congenital heart disease.

Discussion

Terminology. The term myxedema was applied by Ord,[1] in 1880, to the syndrome of "adult cretinism." As is common in other diseases, the outstanding or unusual characteristic of the disease was used as a name for the entire condition. When we speak, therefore, of an individual having myxedema, we refer to the entire syndrome—the slowed mental and physical processes, the dry skin, the brittle nails, the elevated blood cholesterol, the changed protein and mineral metabolism, and the other recognized changes—not to the single feature of myxedematous infiltration of the tissues. Since decrease or absence of thyroid secretion produces the state of myxedema in all of its features, we must consider myxedema as a manifestation of diminished thyroid secretion. Hypothyroidism, and myxedema are, therefore, synonymous terms. To speak of hypothyroidism without myx-

edema, as is occasionally done, is incorrect unless the term myxedema is used in its restricted sense; in which case one could also speak of myxedema without myxedema, using the term first as the name of a clinical entity and then as a description of a specific pathological condition. The expression "hypothyroidism without myxedema" is usually misused in reference to mild cases of myxedema, or, more frequently, to cases of hypometabolism. Myxedema and hypothyroidism imply more than hypometabolism and should not be used in the absence of other evidences of diminished thyroid function.

Symptomatology. When it is recalled that the symptoms of myxedema are all produced by the absence of one hormone and entirely alleviated when that hormone is replaced, it is not surprising that a striking similarity is usually noted in the histories of cases of myxedema. Variations are to be expected in degree rather than in kind. Furthermore, it is unlikely that one symptom or sign would occur without the others being present in about equal degree. If, as recent experience indicates, normal cholesterol metabolism is closely dependent on the presence of a normal amount of thyroxin, we would not expect a markedly lowered basal metabolic rate due to lack of thyroxin without some evidence of altered cholesterol metabolism. The same reasoning applies to the other changes. The occasionally noted variations from this conclusion may possibly be explained in three ways. First, our normal standards for any one sign or symptom are averages from which marked variations must occur and what may, therefore, appear to be normal by our standards may really be abnormal for a specific individual, or vice versa. Second, it is possible that variation may occur at times in the susceptibility of a certain tissue to thyroxin; the tissue may develop an increased sensitivity or an increased refractility to thyroxin. Third, one or more of the signs of diminished thyroid secretion may be concealed by the presence of another pathological condition affecting the same signs in an opposite manner.

Means and Richardson [2] print a table compiled by Krantz showing the incidence of various signs and symptoms; table 1 is in great part derived from that table and shows in outline those symptoms which occur in the majority of cases. Experience indicates that the symptoms of myxedema develop slowly over a period of months and years. Menorrhagia is frequently seen in women in whom myxedema occurs before menopause.[3] M. S. (Case 2) had two uterine curettements with little relief for a symptom that responded readily to thyroid therapy. J. B. (Case 4) illustrates a condition occasionally seen in patients with postoperative myxedema. Although most of the signs and symptoms of myxedema were present—lowered basal metabolic rate, elevated blood cholesterol, dry pasty skin, inability to stand cold, and fatigue—the mental processes were not slowed and were, indeed, more of the type which one might expect with her previous state of exophthalmic goiter. Thyroid medication produced marked improvement. Since her reactivity had always been normal or increased, very little change was noted in this feature; one did, however, feel that her speech and actions were more relevant and consistent than they had been previously.

TABLE I

Myxedema

Symptoms and Findings

General
- (1) Fatigue
- (2) Weakness
- (3) Inability to stand cold
- (4) Weight increase
- (5) Fat increase
  - General
  - Supraclavicular

Skin
- (1) Paleness
- (2) Dryness and scaliness
- (3) Absence of sweating
- (4) Hair—Scanty
  - Coarse
- (5) Nails brittle

Circulatory
- (1) Shortness of breath
- (2) Slow pulse
- (3) Small pulse pressure
- (4) Poor quality of heart sounds
- (5) Dilation of heart
- (6) Electrocardiographic changes
  - Low voltage, especially in T-waves in Leads I and II

Edema
- (1) Eyelids
- (2) Face—cheeks
- (3) Ankles
  - Non-pitting
  - Pitting

Mental and Neurological
- (1) Drowsiness
- (2) Slow speech
- (3) Numbness and tingling
- (4) Impairment of memory
- (5) Impairment of hearing
- (6) Prolongation of tendon reflexes.

Gastrointestinal
- (1) Constipation
- (2) Poor appetite
- (3) Indigestion

Blood
- (1) Increased cholesterol
- (2) Moderate anemia

Lowered Basal Metabolic Rate

Perhaps in this case the nervous system had been so sensitized that it responded to smaller amounts of thyroxin than the other tissues.

The presence of "circumscribed myxedema" in cases of hyperthyroidism has recently been receiving some attention [4] and presents an interesting paradox. Perhaps the explanation is in terms of development of decreased sensitivity to thyroxin in a limited area.

Basal Metabolic Rate. The lowered basal metabolic rate is certainly of great importance in the diagnosis of myxedema. It must be emphasized, however, that a low basal metabolic rate is not of itself an absolute indication that hypothyroidism is present. Many individuals have a basal metabolic rate well within the myxedema range and have no myxedema. The low rate may represent their normal, or some factor other than lack of thyroxin may cause the lowered metabolism.

When the basal metabolic rate falls below minus 20, patients with myxedema usually begin to show mild symptoms—sensitivity to cold, dryness of skin, absence of sweating; but they do not develop the marked symptoms—swelling, mental retardation, cardiovascular changes—until the basal metabolic rate has been below minus 30 for some time.[3] The question of whether symptoms of myxedema can occur with a normal basal metabolic rate is often raised. Patients are occasionally seen who have normal basal metabolic rates and who present symptoms which might be of myxedematous origin and which appear to respond to thyroid. One such case was seen recently in which there was also a somewhat elevated blood cholesterol. When we recall that the basal metabolic rate is influenced by factors other

than thyroid, the possibility of a myxedematous individual with a normal basal metabolic rate would appear to exist. Those cases in which the basal metabolic rate is elevated because true basal conditions were not obtained during the test do not belong in this category but should not be forgotten. An individual whose normal basal metabolic rate is plus 20 or more might show signs of hypothyroidism with a normal basal metabolic rate. A myxedematous individual taking dinitro-ortho-cresol [5] would be an excellent example of a case of myxedema with a normal or even elevated basal metabolic rate. Whether cases might exist in which some substance similar to dinitro-ortho-cresol would be produced spontaneously in an individual having myxedema, thus fulfilling the above conditions, remains for the future to decide.

Blood Cholesterol. Although it has long been known that changes in cholesterol metabolism are associated with thyroid dysfunction, the importance of these changes has only been recognized in recent years. Investigations have shown that the blood cholesterol is usually diminished in hyperthyroidism and almost invariably elevated in hypothyroidism. So consistent is this elevation of the blood cholesterol in myxedema that it has been suggested that the three criteria for the diagnosis of myxedema be (1) the presence of the characteristic symptoms and physical findings, (2) a lowered basal metabolic rate, and (3) an elevated blood cholesterol. To these might be added a fourth, return of the above three to normal under thyroid therapy. It has been pointed out that the efficacy of treatment can usually be predicted on the basis of whether or not the blood cholesterol is elevated. Those cases which have low basal metabolic rates and no signs of myxedema rarely show elevated blood cholesterols and are rarely benefited by thyroid therapy. Hurxthal [6] believes that the finding of hypercholesteremia, in the absence of its few other common causes, points more specifically to thyroid deficiency than does the finding of a low metabolic rate. Determination of blood cholesterol has attained such importance that it may be said that no report of a case of hypothyroidism is complete unless the blood cholesterol value is given. It is interesting to note that in Case 2 the blood cholesterol before treatment, 236 mg. per 100 c.c., might possibly have been considered a high normal. After treatment, however, it fell to 137 mg. per 100 c.c., showing that the initial value represented an increase of more than 70 per cent over the normal value and again emphasizing the importance of variations in normal as an explanation of unexpected findings.

Recent studies of creatinuria in children with hypothyroidism require comment. Until about the age of puberty creatine is normally found in the urine of children of both sexes. In hypothyroidism in children the creatine excretion may diminish or cease entirely. With proper administration of thyroid creatine again appears in the urine.[7]

Carbohydrate Metabolism. A consistent feature of experimental and clinical studies on carbohydrate metabolism is the lack of agreement between

the results of various workers. Several factors probably account for this: poorly controlled experiments, conclusions drawn from too small a number of experiments, and the presence of only a small correlation between the two conditions. The conclusion that in myxedema the tolerance for carbohydrate is increased appears to be commonly accepted in recent literature but cannot be drawn with assurance from the results of experiments on animals.[8, 9] The same is true of work on patients with myxedema without any evidence of diabetes; low blood sugars, normal blood sugars, low prolonged sugar tolerance curves, high prolonged sugar tolerance curves, and other types of curves have been reported. A glaring fault in many of these reports is the small number of cases. Some recent well controlled experiments [10] on hypothyroidism induced by total thyroidectomy indicate that carbohydrate metabolism is not significantly influenced by the hypothyroidism following total thyroidectomy. The belief that the tolerance for carbohydrate is increased in myxedema would appear to rest on two factors: first, it is well recognized that the sugar tolerance is diminished in hyperthyroidism and one would expect it to be increased in hypothyroidism; second, rather definite evidence exists that when diabetes mellitus and myxedema occur in the same individual, the diabetes becomes more severe as the myxedema is treated. It is believed that the decreased severity of the diabetes in myxedema results from the lowered metabolism and does not indicate any antagonism between the secretions of the thyroid and the pancreas. The lack of agreement concerning the effect of hypothyroidism on patients without evidence of diabetes, and the general agreement concerning the mitigating effects of hypothyroidism on diabetes may possibly be correlated as follows: The effect of hypothyroidism, or possibly lowered basal metabolic rate only, is not great enough to be detected by a rather crude test such as the sugar tolerance test because of the great reserve present in the carbohydrate metabolism. When, however, this reserve is lost, as in diabetes, the effect becomes evident.

Shepardson and Wever [11] came to the conclusion, from a review of the literature " that the coincidence of diabetes mellitus and myxedema is probably no more nor less common than could be predicted from the occurrence of the two diseases separately." They also concluded that only 13 cases of diabetes combined with myxedema have been reported in literature. The actual number must be much greater. The family history of diabetes in two of the above cases (Cases 1 and 5) is very interesting. Case 1 is the only one that presented an abnormal sugar tolerance curve. She showed diminished tolerance which was somewhat further diminished by thyroid therapy but not beyond the limits of error of the test.

Change in Reflexes. In 1924 Chaney [12] described the abnormally prolonged character of the tendon reflexes in myxedema. On striking the tendon, the muscle contracts about as rapidly as normally, but remains contracted for as long as a second and relaxes slowly. Chaney apparently

obtained this prolongation in all of his cases of myxedema and considered it to be specific for myxedema since it did not occur in other conditions associated with lowered basal metabolic rates. Although this prolongation of the reflex is very striking and characteristic, it certainly is not always present. Case 1 did not show it or at least did not show it to an extent to be clinically observable. Case 3 showed it at times and at other times gave a quite rapid and normal reflex. When the prolonged reflex is present, it returns to normal with the basal metabolic rate. Figure 5 shows the nature of the reflex as obtained in Case 4 and the improvement with therapy. The prolonged reflex is an interesting sign which may, at times, be of help in diagnosis, but too much importance must not be attributed to its absence.

Blood and Urine. The moderate degree of anemia which occurs in most cases of myxedema has been attributed to the diminished activity which the blood forming tissues share with all the other tissues. It must be remembered, however, that the pastiness of the skin in myxedema is out of all proportion to the degree of anemia, which may be very mild. Some improvement of the blood count and hemoglobin occurs with thyroid treatment but it has been my experience that iron therapy must often be used to bring the blood up to a full normal. In spite of remarkable improvement in all other ways in Case 4, a fairly marked anemia did not respond to thyroid but responded almost immediately to iron.

The urine is usually normal and was so in all of the above cases. However, traces of albumin do occur at times and are of interest only from the standpoint of diagnosis since, as in Case 3, these patients are frequently diagnosed as nephritics.

Gastric Acidity. In spite of some observations to the contrary, the bulk of evidence appears to indicate that there is a definite decrease in gastric acidity in both hyperthyroidism and myxedema.[13] Even more definite is the increase in incidence of achlorhydria in myxedema and a few observations [14] indicate that this achlorhydria is not influenced by treatment (Cases 1 and 5). Interpretation of these findings, should further study confirm them, is difficult.

Cardiovascular Changes. Zondek [15] in 1918 used the term "myxedema heart" to describe a condition found in some cases of myxedema and characterized by an enlarged heart, sluggish cardiac movements and certain electrocardiographic changes. Although "myxedema heart" was at first thought to occur only rarely, recent literature contains ample evidence that it is a common and possibly the usual finding in myxedema. Lerman, Clark and Means [16] believe that "the heart is generally enlarged in myxedema." The incidence of recognition of cardiac enlargement increases with greater care in examination and more frequent use of roentgen-rays. The enlargement, at times quite marked (Case 1), usually involves both sides of the heart. Digitalis has very little influence on the size of the heart, but thyroid therapy decreases the size. The changes which occurred in Case 1 are

shown in figure 1; the small amount of thyroid given in this case (one-half grain daily) is noteworthy. In some cases the heart will decrease in size after thyroid therapy even though it was apparently normal in size before treatment (Case 3). If thyroid is stopped, the heart enlarges; it shrinks again on resumption of thyroid (Case 2, figure 2).

Does the increased heart shadow mean hypertrophy, dilatation, or increased pericardial fluid? The rapid and, in many cases, great decrease in heart size appears to rule out hypertrophy as the entire explanation. Interstitial and intracellular edema, described below, might increase the size somewhat but hardly enough to account for the extent of enlargement which occurs in many cases. Reports of myxedematous patients showing pericardial effusion [17, 18] and especially a case to be reported by Waring, emphasize the part which pericardial effusion may play in some cases. Lerman, Clark and Means [16] feel that "in most cases, however, neither the clinical findings nor the roentgen-ray picture of the heart are consistent with significant amounts of pericardial fluid." We must conclude then that the increase in heart shadow is usually due to cardiac dilatation.

In spite of several earlier reports to the contrary, recent studies indicate that patients with myxedema almost invariably show typical abnormalities in the electrocardiogram and that these changes are favorably influenced by thyroid therapy. They occur even when cardiac enlargement is not present (Cases 4 and 5) and may be considered as early evidences of those alterations in the heart muscle which later may produce dilatation. Flattening or inversion of the T-wave in Lead II is considered the most characteristic change, but flattening of the other T-waves and general low voltage of all complexes in all leads also usually occur. Various other findings have been reported but not as constantly as the above. Many of these changes are illustrated in the cases here reported, all of which showed definite deviations from the normal in the electrocardiogram. These abnormalities usually disappear under thyroid treatment.

If we look for an explanation of the dilatation of the heart, we find that the cardiovascular changes which occur in myxedema can, for the most part, be divided into two groups: (1) those diminishing the circulatory load, and (2) those diminishing the strength of the cardiac contraction. In the former group belong the decreased blood volume and cardiac output. In the latter belong the pathological changes in the heart and blood vessels, the diminished coronary circulation and, possibly, the loss of the tonic effect of thyroxin on the heart muscle. The mild anemia which is often present would be another factor decreasing the cardiac efficiency.

The cardiac minute volume output is markedly diminished in hypothyroidism [19] in the absence of cardiac insufficiency. Of major importance in producing this diminished cardiac output is the decreased blood volume.[20, 21] Thompson [20] calculated that the increase in total blood volume on administration of thyroid to cases of myxedema was not infrequently as

much as 25 per cent. The relationship between the cardiac output and the blood volume is evident in the observation that other conditions remaining the same, the cardiac output varies directly with the volume of circulating blood.[22] As pointed out below other factors are probably also involved in the production of the diminished cardiac output.

Of the factors decreasing cardiac efficiency, the pathological changes in the heart muscle must be most important. Exact information is lacking concerning the nature of these changes because of the dearth of autopsy material on untreated cases and because of our inability to distinguish between those changes due to myxedema and those due to commonly associated conditions most important of which is arteriosclerosis. Experimental work in animals must be interpreted with caution. Changes due to myxedema can be divided into those that are reversible, that is, disappear on giving thyroid, and those that are irreversible. Possible reversible changes in the myocardium are (a) interstitial edema, (b) intracellular edema, and (c) a moderate degree of granular degeneration. Among the irreversible changes is the degeneration of the muscle fibers described by Webster and Cooke [23] and others. The changes produced by such complicating factors as arteriosclerosis and hypertension and exemplified by coronary sclerosis and myocardial fibrosis are of course irreversible.

Although it appears to be generally assumed that the coronary blood flow in myxedema is decreased, attempts to analyze the possible changes in the light of modern conceptions of the mechanics of coronary flow would seem inconclusive. In a denervated heart preparation, the mean pressure in the aorta appears to be the most important factor determining coronary blood flow.[24] Since in myxedema the diastolic pressure is usually increased and the systolic pressure very often somewhat increased, if blood pressure were the only factor, coronary blood flow might also be increased. In the intact heart preparation, however, a reflex nervous mechanism apparently keeps the coronary blood flow proportional to the cardiac output.[24] Since the cardiac output is greatly decreased in myxedema, a diminished coronary flow is to be expected. The influence of other factors, such as, rate and strength of contraction, and muscular tone cannot be properly measured in our present state of knowledge. Essex and his co-workers [25] state that thyroxin augments the coronary flow as much as 300 to 400 per cent over the control values. The extent of the increase is so great that it would appear that some specific effect might be involved. Since decrease in cardiac output is the most marked change and since this decreases coronary flow it is probable that the final effect is a diminished coronary blood flow.

Yater [26] and others have shown that thyroxin stimulates the heart muscle producing an increase in heart rate. It is quite possible, although not proved, that it may also exert a tonic action on the heart. Yater advances the hypothesis that the increased circulatory output in hyperthyroidism is not a result of the increased need of the tissues for oxygen but a fortuitous

circumstance resulting from the stimulation of the heart by thyroxin. Without entering upon a critical analysis of the theory, we may advance the corollary in regard to myxedema. The diminished circulation in myxedema would thus be considered, not as an adjustment of the circulation to a diminished oxygen need, but a fortuitous condition arising from the lack of thyroxin to stimulate the heart. The decreased blood volume, described above, and the poor venous return resulting from the diminished muscular activity and lowered skeletal muscle tone would further lower the cardiac output. In favor of this hypothesis is the lack of correlation between the lowered basal metabolic rate and the decrease in cardiac output [19]; the cardiac output is decreased more than would be expected and an increase in the arterio-venous oxygen difference is produced.

The incidence of hypertension seems to be greater in patients with myxedema than in the general population.[16, 27] On treatment the fall of blood pressure in those patients showing hypertension is apt to be marked and in a large proportion it returns to normal. Occasionally a patient showing a normal blood pressure before treatment may become hypertensive under thyroid therapy. Although hypertension when present means an added load on the heart, the possibility that it may represent a compensatory mechanism must not be forgotten.

Having examined the changes which increase and also those which decrease the load of the heart, we may follow Hallock [28] in his explanation of the dilatation of the heart. The pathological changes in the muscle, the diminished coronary circulation, the loss of the tonic action of the thyroxin, and the mild anemia tend to diminish the strength of the cardiac contraction —to make the heart hypotonic. Although the diminished blood volume and circulatory output decrease the work of the heart, in some cases they do not balance the harmful factors and the heart cannot carry on its work without in some way increasing the strength of its contractions. This it can do by increasing its diastolic size since according to Starling's " law of the heart " the greater the initial length of the muscle fibers, that is, the greater the diastolic size of the heart, the greater the force of contraction. The heart, therefore, increases its diastolic size.

We must leave Hallock at this point to consider another phase of the problem, the relation of venous pressure to cardiac dilatation. Increased venous pressure is the price that the heart usually pays for the increase in size which permits it to contract more strongly. This will be made more evident if we examine Harrison's concept of the cause of increased venous pressure in the pulmonary circuit [29]: If the left ventricle is working against a load (or if, for any reason, it cannot contract as efficiently as previously) it does not expell the usual quantity of blood. Since it is still receiving the same amount, the blood collects in the ventricle and its diastolic size increases. With increase in size, its strength of contraction increases and it now expells its original amount. As the left ventricle dilates, however,

the pressure in it rises a little toward the end of diastole and the left auricle, now working against this greater pressure, fails to empty itself completely and blood collects in it until, in spite of its distensibility, the pressure increases. As a result of this increase in pressure in the auricle, less blood enters the auricle than formerly. Since the right ventricle is still expelling the same amount, the blood accumulates in the lungs and the pressure in the pulmonary circuit increases. This rise in pressure now corresponds in degree to the increase in the pressure in the left auricle. It can thus be seen that the origin of the increase in venous pressure in the pulmonary circuit (pulmonary congestion) is in the resistance of the muscle fibers of the left ventricle to stretching. If in the foregoing illustration the muscle fibers of the ventricle could have stretched without requiring an increase in the pressure in the ventricle toward the end of diastole, there would have been no need for increase in pressure in the auricle and no resulting pulmonary congestion. The factor involved might thus be considered a sort of " stretching resistance " of the muscle fibers, or a " filling resistance " of the heart. This resistance to stretching may depend upon a sustained partial contraction of the fibers (muscle tonus) or upon the elastic properties of the fibers and would vary with changes in either. Because of this " filling resistance," dilated hearts, beyond a certain degree, are ordinarily accompanied by signs of congestion, that is, signs of increased pulmonary or systemic venous pressure. If, then, the " filling resistance " is normal in myxedema we would expect to find congestive signs with moderately or greatly dilated hearts.

Congestion in the pulmonary system would be evidenced by diminished vital capacity, dyspnea, orthopnea, increased pulmonic second sound, basal râles, and cough. Vital capacity studies have not as yet been complete enough to give definite evidence for or against the presence of congestive failure in most cases. The observation [21] that the vital capacity was strikingly diminished in myxedema in the absence of any signs of congestive heart failure, and did not show significant changes following treatment makes any interpretation of vital capacity studies difficult. Dyspnea is one of the earliest evidences of congestive failure but as it can be produced by other causes it cannot by itself be considered as absolute evidence of congestive failure. Its frequency in myxedema may be otherwise explained. Of primary consideration is the patient's frequent confusion of shortness of breath and fatigue. The latter is a marked and universal symptom in myxedema and close questioning will often reveal that what was considered shortness of breath is really fatigue. With diminished blood volume, and with inadequate venous return as a result of poor muscle tone and diminished and poor contraction of the skeletal musculature, it is possible to have dyspnea on the basis of inability to increase cardiac output from a form of peripheral failure. Orthopnea is only rarely described as a symptom in myxedema. The pulmonic second has not been mentioned as accentuated.

Basal râles and cough are occasionally present but usually no more frequently than might be expected from causes other than congestive failure.

Evidences of increased systemic venous pressure are indicated by distended cervical veins, increased venous pressure measurements, peripheral edema, and enlarged liver. Distended cervical veins are only occasionally noted in the literature. They were not seen in Cases 1 and 2 above. Where reports of venous pressure measurements are mentioned they have usually been normal. The work has, however, been done in most cases on patients with normal sized hearts and with no signs of venous congestion. Altschule and Volk [19] found that the venous pressure remained normal in three cases of postoperative myxedema in which the heart enlarged with development of the hypothyroid state. Pitting edema around the ankles occurs in a large percentage of the cases of myxedema including many cases with hearts of normal size. Since edema on a cardiac basis does not occur, with rare exceptions, unless the heart is dilated, we must assume that in most cases of myxedema the edema is on a non-cardiac basis. Edema, when present, may be on the basis of local circulatory changes such as poor venous return due to poor muscle contraction and tone, on interference with venous return due to fatty and possibly myxedematous deposits, and on local tissue changes. The presence of an enlarged liver which diminishes in size after treatment is occasionally reported.

It can thus be seen that in only a small percentage of the cases of myxedema with cardiac enlargement can the signs and symptoms be considered as conclusive evidence for the presence of congestive heart failure and that in most cases one need not assume the presence of congestive failure. We have then a condition in which the heart is dilated, often greatly, and it has done so without paying the price of increased venous pressure; in other words, the " filling resistance " is decreased. This may possibly result from a loss of the tonic effect of thyroxin or from changes in the elastic properties of the muscle fibers produced by the absence of thyroxin. Even more definite evidence of this decrease in the " filling resistance " may be found in cases of congestive failure treated by total ablation of the thyroid. In some of these cases improvement, decrease or clearing up of the symptoms of congestive failure, may occur even though the heart continues to dilate [30]: that is, the same or a greater degree of dilatation may be present with a lower venous pressure. The improvement in these cases is usually ascribed to the diminished demand on the heart which results from the lowered metabolism. Although the importance of this factor is evident, it does not explain how the heart can maintain the same size or even become larger while the venous pressure decreases. The heart in these cases must have less " filling resistance," permitting dilatation with a smaller venous pressure. If by the induction of hypothyroidism in these cases of circulatory failure, the circulatory load is diminished and the heart permitted to maintain its same size with a lower venous pressure (thus giving it the advantage of increased

diastolic length), and if the pathological changes resulting from hypothyroidism are kept at a minimum by not permitting too low a basal metabolic rate, the improvement often seen can easily be explained.

The foregoing discussion may be summarized as follows: The changes in the heart produced by lack of thyroid tend to make the heart hypotonic. At the same time changes occur in the muscle fibers which permit them to stretch more easily and give the heart a diminished "filling resistance." If the hypotonicity is great enough to require a greater initial length of the muscle fibers to produce an adequate contraction, the heart dilates, but since the "filling resistance" is diminished it does so without increase in venous pressure and without congestive changes. If pathological changes, such as arteriosclerosis, hypertension, or rheumatic heart disease are present, congestive failure may occur either because the dilatation is sufficient to produce increased venous pressure in spite of the lower "filling resistance," or because the "filling resistance" cannot diminish as much in an hypertrophied or fibrotic heart as it does in a normal heart.

On treatment with thyroid, various results might be expected. If the pathological changes are reversible, the heart size may decrease as a result of the improvement in tonus. If the pathological changes cannot be reversed by thyroid, the individual may become worse since the "filling resistance" and the circulatory load are increased; congestive failure may result or become aggravated. In some cases the factors may balance and the condition remain the same.

Treatment

Many cases of myxedema are quite sensitive to thyroid and only small doses are needed to produce marked changes. This is very nicely illustrated in Case 1. It has been said that the more thyroid an individual can tolerate, the less hypothyroid he is. In view of the marked cardiac changes which are frequently present, the necessity of increasing the basal metabolic rate gradually and permitting the heart to adjust itself to the changed load is obvious.

Various brands of thyroid contain different amounts of iodine and show some variation in strength. Furthermore, some firms label tablets according to the amount of fresh gland present and others according to the amount of dried gland present. Since one part of dried gland is equivalent to about five parts of fresh gland, this difference must be remembered; for example, a five grain B. W. and Co. tablet is approximately equal to a one grain Lilly tablet.

Finally, since "the effects (of thyroxin) start only a day after administration, even with intravenous injection, and then continue to increase, reaching their maximum in about 10 days, after a single dose,[31]" it is useless to give thyroid in broken doses during the day.

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INFANTILE CEREBRAL PALSY; ITS TREATMENT BY SELECTIVE INHIBITION OF SENSORY STIMULI *

By Earl R. Carlson, M.D., *New York, New York*

When the nervous system has been damaged by disease or injury at birth and choreo-athetosis, spasticity, ataxia or some other type of hyperkinesia is present, the tendency in prescribing treatment is to place too much emphasis on physical training without due consideration of the effect that repetition of an activity has upon the growth of the behavior pattern at various stages of development. Stepping movements, for example, show themselves almost immediately at birth but no amount of exercise is going to enable the normal infant to walk until his nervous system has attained adequate differentiation. In the case of the cerebral palsies there are also limits circumscribed by anatomical and physiological growth beyond which no amount of exercise will help the patient and in fact the overdoing of such exercise may even lead to greater difficulties, as for instance, in the case of the mother who ties up the good hand of the hemiplegic child thinking that the more he uses the maimed member the sooner it will be normal. She often creates speech disorders and behavior difficulties which are far more serious than the original handicap. Now and then one comes across a spastic whose physical training has been almost negligible, who becomes an author, a teacher, an attorney, a librarian or a successful business man in the face of what seem to be insurmountable difficulties, while another spastic whose physical affliction is slight in comparison and who possesses average intelligence becomes anti-social in spite of having had supposedly the best of muscle training, all of which makes one feel that the more important part of treatment has been neglected, namely that of developing the assets which the child already has at his disposal and aiding him in adjusting to his handicap and the conditions of life as he finds them. As the child develops the unimpaired areas of his brain and acquires outside interests, there is a corresponding improvement in muscle control, as is exemplified in the case of the spastic girl who is so muscle conscious during meals that she cannot feed herself but nevertheless is able to forget herself in music to the extent that she plays the piano most satisfactorily. The fact that a spastic athetoid is able to maintain perfect control of his muscles when fear, anxiety and self-consciousness are in abeyance should be evidence enough that progress in the treatment of such conditions does not rest in exercises which will make the patient all the more muscle or speech conscious but rather in applying measures that will tend to reduce to a minimum the number of sensory stimuli to which the patient is unaccustomed to attending simul-

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taneously. In this paper I shall relate observations on the effect of sensory stimuli on muscular activity in cases of cerebral palsy.

During sleep, when sensorial impressions are reduced to a minimum, the purposeless movements cease and the muscles invariably attain relaxation even in the worst cases of spasticity and athetosis. Contrary to one's expectations, after a good night's sleep, the patient is usually worse during the morning hours. A mother will relate that her child is unable to feed himself at breakfast but finds little or no difficulty with the evening meal. The thought processes are also reflex activities and in the case of the spastic athetoid may be as hyperactive as the knee jerk. His power of concentration is therefore limited, and is reflected in overflow motor activity, which grows less as the child gets into the routine of the day's play or work and the sensory stimuli, which his nervous system is unaccustomed to handling simultaneously, are lessened. The value of an academic program in helping the spastic athetoid of good intelligence cannot therefore be overemphasized. Parents who delay academic training until the child acquires better control of his hands or speech are surprised at the rapid improvement in muscle control which follows when the child is finally allowed to go to school.

When the spastic athetoid emerges from a deep sleep to the waking state and is suddenly confronted with more sensory stimuli than his defective nervous system can adequately handle, we find a corresponding sudden change from a state of complete muscular relaxation to a state in which the patient exhibits his least ability to control muscular movements. If the change from sleep to the waking state is more gradual, as for example during the recovery from the effects of ether anesthesia, the patient's ability to control his muscular movements will be at its best when he emerges from the ether and will become progressively worse as the effects of the ether wear off. In taking histories of cases of choreo-athetosis with and without spasticity, it is a common experience to find that patients or their relatives volunteer that much of the choreo-athetosis and spasticity have been lost for a short time after recovery from ether anesthesia after surgical operations. One mother related that the first time she had ever been able to understand the speech of her spastic athetoid and dysarthric child was when the child was recovering from the effects of ether following a tonsillectomy. I have had occasion to witness a child under similar circumstances. There was little or no dysarthria when the child was coming out of the effects of the ether. As the ether wore off the child's words became less and less distinct and finally the speech became as dysarthric as before the operation.

In an illustrated lecture before the American College of Physicians in 1936, I showed movies of the effects that alcohol had on controlling athetosis and spasticity in the case of a man of 45 years of age. He was unable to bring a full glass of water to his lips without spilling half the contents. After drinking two ounces of whisky he was able to handle a full glass of

water without difficulty. At no time during the alcohol experiment was any evidence present of impairment of intellectual processes, of dullness, stimulation, euphoria, or loquaciousness. The patient was not an addict to alcohol although he had been aware of its effects for many years. The subjective feelings of one such patient were interesting, his comment being: "Alcohol does not necessarily make me do things better, but makes me forget the things which I do badly." Another comment was: "My friends tell me that I am more drunk when I am sober than when I have had a drink."

The majority of observers have explained the origin of choreic and athetoid states on the basis of basal ganglia damage. There is reason, however, to speculate as to their possible cortical origin. Suffice it to say that the effects of alcohol are supposedly those of reducing the activity of the higher centers of the nervous system. Under the influence of alcohol, the lower centers (basal ganglia) retain a certain degree of autonomy and can carry on their functions without being influenced by the damaged cortex. It is difficult to explain the observations made unless one accepts the theory that alcohol diminishes the domination of the higher cortical structures over the dependent and phylogenetically older lower centers. Possibly the mechanism is an elevation of the sensory threshold by alcohol and a corresponding reduction of the number of sensory impulses reaching the higher centers.

If choreo-athetosis and spasticity can be abolished through administration of ether or alcohol, then other measures of cutting down sensory stimuli should be equally effective in controlling adventitious muscular movements. It must be emphasized, however, that these stimuli are not to be eliminated altogether but should be reduced to the minimum necessary for the production of a well coördinated motor act. In the case cited above of the athetoid child who spoke better when under the influence of ether, too much of the drug caused cessation of all activity and too little was without effect—but when the concentration of ether was such that sensory stimuli were depressed just enough, then the act of speaking was almost perfect.

McGraw made observations on the behavior of the normal infant who was just beginning to extend his arms to reach for an object in the visual field. She showed that if the sight of the object is excessively stimulating the energy which should be directed toward extension of the arm in the direction of the object becomes converted into disorganized general body activity. Too little interest in the object would fail to stimulate movement in the direction of the object and too much interest would interfere with the individual's control over the motor activity involved. It is desirable that the individual should be interested in the object just enough to elicit a well controlled motor act. McGraw found that if the child was allowed to handle the object before reaching for it and thereby increase his sensory

experience the excess motion in the reaching prehensile act would be eliminated.

I made a related observation in the case of a spastic athetoid patient who was given blocks to pile up on a table. He placed the first one on the table with only slight athetosis. The placing of the second block on the first was done with an increased amount of overflow activity, which was further augmented when the third was placed on the second. The fourth could not be placed at all and the whole pile was knocked down. This was repeated several times with more or less the same results. The patient was then made to wear a pair of partially opaque glasses which cut down his vision to the blocks and the immediate vicinity of the table. He was then, after a few trials able to place one block on the other without as much overflow and was able to pile more blocks than before. One must not draw the conclusion from this that merely fitting a pair of dark glasses to such a patient is going to relieve him of all his athetosis, but it does show that in this particular case excess visual stimuli did play a considerable part in the production of overflow activity. I was impressed by the effect that cutting down visual stimuli had in enabling an athetoid young man to feed himself in the presence of others who were watching his grotesque muscular movements during a meal in a restaurant. The more apprehensive he became of the people watching him, the greater was his difficulty. Being very myopic, he removed his glasses and not being able to see the others as well as he did before, he finished the meal without any trouble.

In helping a spastic athetoid to use his hands, it is often surprising to find how a slight pull over a muscle or tendon (proprioceptive sense) will prevent an overflow of muscular activity and will enable the patient to maintain perfect control as long as we keep the pressure there. By means of using a small iron disc fastened with adhesive tape to the skin I have through the force from the electro magnet on that disc been able to study the effects of a pulling force on a particular muscle group. In a subsequent paper, I shall report these findings.

The spastic athetoid has difficulty in correlating muscular activity and perception. He tries to look in too many directions at once. In shaking hands he thrusts his hand out aimlessly. If before shaking hands he is asked to look sharply at the thumb of the hand he is trying to reach, he will have no difficulty in shaking hands. Speech is likewise improved when the spastic athetoid focuses his eyes at a certain point in speaking. This is one of the reasons why lip reading is valuable in helping the general type of dysarthria present in spastic athetoid cases. If the person has to read lips he will obviously have to look at the one whose lips he is reading and in so doing he cuts down his vision with a consequent decrease in adventitious muscular activity. In learning to walk, the patient looks in every direction except where he is walking. This was illustrated in an athetoid case with considerable ataxia. In attempts to walk, the patient would stagger along

like a drunkard not looking in the direction of his walking and holding his arms flexed at the elbow and wrist. When he was told to focus his eyes steadily at a point in the direction of his walking, the overflow movements ceased, his gait became better and the arms came down to his sides without the patient being told to bring his arms there. When this same patient had to walk in total darkness, he became terrified and could not take a single step without falling. One dark evening when this patient was walking outside in a pair of white shoes, I noticed that his gait was better than I had ever seen it on previous occasions. The darkness of the night in cutting down his vision to the white shoes and the road, eliminated excessive motor activity. Here we have a child who is hardly able to walk in full daylight, is not able to walk at all in total darkness and yet, is capable of obtaining an almost normal gait when the visual stimuli are cut down to the proper amount.

According to McGraw the origin of many childhood " fears " may be attributed not necessarily to some unpleasant experience and its resultant associations but to a natural growth imbalance or lack of integration between several aspects of development. A child walking in the dark will show muscular tensions if his perceptive development is at such a stage that it does not integrate smoothly with the motor adjustments involved. This attitude may persist until it constitutes a " fear " of the dark. If the child's experiences are treated casually, the tension resulting from normal growth imbalance will soon fade except to the extent that a degree of tension may be needed for handling the situation. If a natural growth imbalance contributes to the development of an attitude of fear in the normal child, how much more should not such a factor be responsible for producing a similar attitude in cases of cerebral palsy where disease or injury is primarily responsible for growth imbalance.

Studies by Brickner and Lyons on individual acquired automatic associated movements in cases of encephalitis show that the organism remembers the acquired acts while instinctive acts are impaired. They cite as an example the case of a man who was a star pitcher for the New York Giants until six years before when he contracted definite and typical epidemic encephalitis. He is able to walk only with difficulty and all his routine motions are made with the usual retardation. In their test the man stood on the lawn of the hospital, his head and shoulders stooped, his hands trembling, his whole attitude one of characteristic rigidity and immobility. But when a ball was thrown to him, his whole body immediately became plastic, he made a perfect catch out at the side and at once threw the ball back. The whole act was characterized by a beauty and grace not attainable by the ordinary normal man. Brickner and Lyons state that " specific acquired acts in which grace and automaticity were achieved by the individual patient, prior to the onset of the illness can still be executed by patients with epidemic encephalitis despite rigidity."

In the introductory paragraph of this paper, the case of a spastic girl was mentioned, who is so muscle conscious at meal times that she is unable to feed herself, but is nevertheless able to forget herself in music to the extent that she plays the piano quite satisfactorily. Mention should also be made of a bacteriologist who has great difficulty in feeding himself but is nevertheless most successful at his profession. Still another case is that of a spastic athetoid whose difficulty is in feeding himself and yet he is able to play golf and compete with many normal men; in fact, his ability is so great that he might some day become a professional. The ability of the encephalitic to catch a ball in spite of rigidity and the ability of the congenital spastic athetoid to play the piano in spite of not being able to feed herself, suggest that the factor for the preservation of skilled acts in the case of the encephalitic must have something in common with the factor for acquiring a skilled act in the case of the spastic athetoid. This common factor is of interest.

The beginner at the piano may experience as much difficulty in placing the right finger on the right key as the spastic athetoid does in learning to handle a cup. Through practice the piano player learns to limit movement to certain muscles and eventually is able to play a well practised piece without much conscious effort. The difference between a normal person acquiring a skilled act, such as playing the piano, and the spastic athetoid learning to handle a cup is not so much a matter of complexity of muscular movement, as it is direction of attention upon the purpose of the act. The pianist is not interested in muscle training per se, but in a purpose; he wants to play and his muscular skill increases as he forgets himself in his music and learns to play without conscious effort. The hand of the spastic athetoid likewise becomes more agile as he forgets himself in his work. This is illustrated in the case of a chemistry student with a bilateral athetosis. He could hardly feed himself when he entered college. Through studying chemistry he developed considerable manual dexterity. When he started laboratory work, fear of acid burns made him spill solutions although he had no difficulty in handling two empty beakers. As he learned to pay more attention to the chemistry problem involved in his laboratory work, fear abated and manual control increased. The manual ability thus gained meant more to him than any amount of conscious muscle training he had ever undertaken.

The value of routine exercise cannot be determined by how well the spastic athetoid performs in the treatment room. I know spastics who perform splendidly in an environment to which they are accustomed but who go all to pieces when confronted with new situations. The spastic therefore needs something more than physical training to fortify him when he faces the new conditions of life and is confronted with more sensory stimuli than he can adequately take care of.

Merely to teach him to let go of his tense muscles by thinking of a rag

doll on such occasions is not going to solve his problem. Neither will ether, alcohol, luminal or other sedatives, in spite of their effects on cutting out sensory stimuli, yield any permanent results. The patient must develop the assets which are already at his disposal. As these assets are given opportunity to develop, the patient begins to feel that he is an integral part of society instead of an ostracized member. His greater assurance and confidence will make him more oblivious of his condition and less apprehensive of his shortcomings, all of which tend to minimize the sensorial input with a consequent increase in equanimity.

We are becoming more aware of the importance of vocational guidance and of the direction of the education of normal children towards equipping them to enjoy a full life. The value of providing the child with the means of manifesting its ability in one way or another has long been recognized. Why should we not have schools which, in addition to providing physical training, will be equipped also to enable the spastic to gratify in acceptable ways his desire for personal worth? The spastic athetoid who sits all day waiting for his next exercise and watching the activities of normal children cannot help but develop an attitude of anxiety or resort to daydreaming instead of the contemplation of reality. Such a child is helped by placing him with a group of handicapped children of average mentality assuming that his rating is such that he can learn to compete and develop a sense of importance.

The delay in the mental development in the spastic athetoid group is usually attributed to the lack of that type of mental growth which is stimulated by grasp and touch in every normal child. I feel that the reverse is truer; that is, the defect in muscular control is accounted for by the lack of a rounded education program for that child. The aim of such a program should be to develop objective interests which lead to the cutting down of sensory stimuli to those connected with the act that the patient is performing. The spastic athetoid cases mentioned above who have difficulty in feeding themselves and yet are able to do skilled acts satisfactorily like playing golf, playing the piano, and working out problems in chemistry and bacteriology behave in such fashion because such activities hold their interest whereas feeding is such a routine procedure that they are unable to develop interest in the act sufficiently to forget the things they do badly.

Between 15 and 20 per cent of crippled children are victims of intracranial hemorrhage. In some states the percentage is as high as thirty. It is maintained that nearly all of such cases develop serious behavior difficulties later in life. In the spastic athetoid group an estimate of the intelligence is often obscured by the muscular defects to the extent that they may be falsely regarded as completely defective in mentality or as possessing normal mental potentialities capable of development under physical training. It is pathetic enough to see a mother bring a mentally defective cripple to the clinic for physical training year in and year out in the hopes that as he gets

the use of his hands his intelligence will increase proportionately and will eventually approximate normal. But nothing is more heartbreaking than an intelligent child with a spastic arm or leg approaching adolescence who in spite of having had the best muscle training is rapidly becoming markedly introspective because of his inability to adjust to his handicap. In some instances the milder the physical affliction the more severe is the mental handicap. When faced with new situations, the spastic generally takes the easiest way out. In school the teachers are lenient with him and should he not know the answer required it does not take much effort to appear more nervous than usual and thus invariably the teacher refuses to press him, taking it for granted that he knows the answer.

I know one successful business man who completed high school in that way. He attributes his success not to his feigning in high school but to a strict master in college who would not let him hide his ignorance behind an exaggerated athetosis. The result was that he had to repeat his first year in college. He was given every opportunity to prove his worth. Extended time was allowed him in taking examinations but he had to learn to face reality. He had to recognize the fact that the things he had formerly been praised for—such as ability to bring a cup to his lips without spilling, an act expected of everybody without comment—did not constitute the things of major importance in life. The spastic is often made to feel that his main purpose in life is to live to get well, rather than to learn something that will compensate for his afflictions. Is it any wonder then that we read such sweeping statements to the effect that two-thirds of the cerebral palsies are mentally defective? And this refers not only to the severely handicapped; but as well to those so slightly motor handicapped that they cannot be called crippled.

In discussion of the latter group, it is often mentioned that they are unable to progress from the infantile stage. Intellectually function may be little impaired, while effectively these individuals show disturbance or even incapacity of judgment and practically behave as weak-minded. Their social adjustment is interfered with because of their proneness to an attitude of foolish cheerfulness, of nonsensical levity, or of lack of reserve, which their vain self-satisfaction accentuates. Such cases are probably much more frequent than would be noted merely from those who fall under clinical observation, since the physical affliction is so slight.

To dismiss this group and say that nothing can be done for them because their anti-social behavior can be explained by a slight intracranial hemorrhage is as absurd as thinking that the one armed man cannot adjust to his handicap and become a useful citizen. I have seen many such children become socially adjusted through placing them for a time with a physically handicapped group with whom they can learn to compete. Having once gained self-assurance and confidence that their inferiority can be adequately compensated for, they feel their worth is proved. This belief can then be carried over into other situations.

One striking example is the case of a boy of 12 years whose muscular handicap was so slight that it was noticeable only when he became embarrassed or had to face new situations. In school he did not get along well and was several grades behind his age. He complained of headaches and had to be excused from class several times a week. By placing this boy with a group of handicapped children of average intelligence where he was able to show them how to play ball and swim, it did not take long until he was up to the average class. What he gained at camp he was able to carry over most satisfactorily in a normal environment.

The problem of the cerebral palsy child, and this can also apply to the nervous child in general, is not going to be solved by establishing large hospital schools where hundreds of such cases can be taken care of. Such a child needs guidance in helping him meet new situations, and not institutionalization. There are adequate facilities in most of our larger cities for diagnosing and prescribing treatment for the birth injured but the prescription is one that cannot be filled in the corner drug store. The establishment of special schools running in conjunction with the local board of education where the mental and physical development can be simultaneously controlled will enable the child to receive the prescribed treatment. There should be a centralized hospital school for diagnostic and teaching purposes where parents and teachers can be instructed in handling these cases. Cases accepted for education and treatment in these schools should be selected according to the severity of the lesion, the age of the patient, the degree of the intellectual impairment, whether a progressive disorder or whether a hereditary affliction. This calls for not only careful clinical examination to detect the special disabilities but also careful analysis as to the intelligence rating. At times encephalogram studies and careful psychiatric and sociologic investigation are necessary.

Since the infantile cerebral palsies do not constitute a single disease with a single etiology, a detailed history is necessary to rule out the progressive types of disturbance which are not amenable to therapy. The severity of the lesion or the diagnosis of the condition in doubtful cases can be estimated frequently by the use of the encephalogram. This proved to be the case when identical twins with a history of instrumental delivery accompanied by cyanosis, a disturbance of gait, speech and general incoördination were presented for observation. Had only one twin survived, the conclusion would have been that the condition resulted from birth trauma but the evidence of identical twins with identical brain defects, which encephalograms revealed, made any other cause than failure of development impossible. Obstetrics is often unjustly blamed for producing many of these conditions. While we should manifest a greater concern to the ends of encouraging better prophylactic measures and after treatment, at the same time it is important to bear in mind that unless the factors contributing to the cause of the disturbance are more accurately ascertained, and no one is un-

justly blamed for producing the condition, we are not going to get the co-operation of physicians in stimulating interest in the establishment of schools where cases of infantile cerebral palsy can be properly trained. Neither must it be concluded that just because we make a diagnosis of birth injury we are dealing with a fixed type of brain injury. Dyke, Davidoff, and Masson have shown that a porencephaly due to trauma may cause a progressive type of disorder. A traumatized nervous system, on the other hand, is more susceptible to infections and not infrequently there may be a superimposed encephalitis. At adolescence the difficulties are sometimes accentuated because the patient then becomes more conscious of his affliction. Aside from the progressiveness or non-progressiveness of the disturbance a clinical examination should reveal what contributes to the status which the muscles are in. Is the atrophy one of disuse or has the lesion interfered with the nutritional centers of the brain? It is not only necessary to know whether the muscles are spastic, athetoid, ataxic, etc., but more important is to know the type of sensory stimuli which tends to keep them in that condition. We have mentioned the importance that visual stimuli play in learning to walk, to control the hands and in talking. It is often surprising to find that a patient who has never been able to walk will do so shortly after the surgical correction of a strabismus. I have also seen head shaking and other adventitious movements disappear after muscles necessary in controlling the eyes have been treated. Almost 15 per cent of the cerebral palsy cases which have come to my attention have definite impairment of hearing, sufficiently to interfere with their speech development and education. They are not deafmute, or aphasic. Just as color-blind persons are blind to one end of the spectrum, so others may be deaf to one end of the tonal scale. There are special methods for diagnosing and treating such conditions. Obviously if a person with cerebral palsy has a reading disability or educational difficulty he is not going to profit from the ordinary classroom routine, and special training in addition to his muscle therapy has to be devised. Care must therefore be exercised in differentiating between a special disability and a deficiency. The latter is not amenable to treatment, whereas a special disability, such as in speech and in reading and writing, can often be overcome under proper training.

The treatment of infantile cerebral palsy in contrast to that of anterior poliomyelitis requires that more attention and thought be given to the sensory side of the reflex arc. In this paper an attempt has been made to show the influence that selective inhibition of sensory stimuli has on the patient's ability to control his muscles. During sleep the adventitious muscular movements cease. The effects of ether, alcohol and sedatives were mentioned. The effects of reducing or concentrating visual stimuli in talking, walking and use of hands were noted. The effect of selective inhibition of sensory stimuli by developing interests in piano, golf, chemistry and bacteriology was pointed out.

In conclusion it may be said that those natural or environmental stimuli which affect the normal individual also affect the cerebral palsy. Indeed it is indisputable that the cerebral cortex receives these stimuli, visual, auditory, proprioceptive sense, etc., summates these stimuli and transfers them to their proper channels for their final release through motor or other pathways. In the cerebral palsies where there is considerable damage to the cerebral cortex and the ideational centers are preserved these stimuli affect the injured brain in a manner shown in the individual cases. A shunting of one or more sensory stimuli will affect the cortex in degrees and thus the final release will be somewhat more towards the normal, as for example, the spastic athetoid cases mentioned who have great difficulty in doing simple acts like feeding themselves and yet are able to do skilled acts satisfactorily like playing golf, playing the piano, and working out laboratory problems in chemistry and bacteriology. With educational training new channels of release will be provided, a partial inhibition of sensory stimuli will be accomplished, and in due time a summation of these sensory stimuli will result in more or less the normal manner.

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THOUGHTS ON HYPERTENSION *

By DAVID RIESMAN, M.D., Sc.D., LL.D., F.A.C.P.,
Philadelphia, Pennsylvania

WHETHER hypertension is a disease or a symptom is a much debated question. It can, I believe, be answered rather easily, for the present at least, in the following way. When we know the cause or the apparent cause we emphasize it and consider the hypertension as part of the symptom complex. When we do not know the cause we look upon the hypertension as the disease itself. On this basis such hypertension as that of chronic nephritis or aortic insufficiency is a symptom, while that of unknown cause is a disease entity. Such a disease entity is represented by essential hypertension.

Although my main object is to deal with essential hypertension, I shall for purposes of clarity give a tentative classification of hypertension. As long as our knowledge of the etiology is limited, such a classification has to be mainly clinical.

CLASSIFICATION OF HYPERTENSION

1. Primary, essential or arteriolospastic.
2. Arteriolitic or malignant.
3. Nephritic.
4. Secondary or accidental.
   - (*a*) Aortic insufficiency
   - (*b*) Coarctation of the aorta
   - (*c*) Adrenal tumors
   - (*d*) Pituitary basophilism
   - (*e*) Hyperthyroidism
   - (*f*) Pregnancy
   - (*g*) Enlarged prostate
   - (*h*) Arteriovenous aneurysm.

Subclasses:

1. Juvenile
2. Superhypertension

I need say little about this classification—it is largely self-explanatory. With regard to malignant hypertension, I might say that I do not believe it is a late stage of essential hypertension. It is a different disease and has all the earmarks of a distinct clinical entity. In my experience it has occurred earlier in life than essential hypertension. The diastolic pressure is much higher than in the majority of cases of the latter. Renal changes are pronounced. The peripheral vessels are thickened, tortuous, tense and hard.

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Retinal changes are present. The patient looks pale and sallow; his color has been compared to that of a cold buckwheat cake. Cerebral accidents are common.

On account of the necrotic inflammatory changes in the arterioles, the term arteriolitic hypertension is applicable.

The secondary types of hypertension need not detain us, except to say that the hypertension in some of the conditions is compensatory; in others, the connection between cause and effect is obscure.

Juvenile hypertension and superhypertension are entirely arbitrary classifications. By juvenile hypertension I mean a premature hypertension occurring usually from just before puberty to about 35 years. My associate, Dr. Stanley E. Harris, has found many instances among students at the University of Pennsylvania and I have seen a number of examples in my office. We admit to this class only those cases in which the blood pressure has been repeatedly tested and found elevated—150 and upwards.

Superhypertension is applied to those cases in which the blood pressure is 260 and higher. I have put them as a separate class so that I can better watch them and note their progress. Such a procedure will eventually be helpful in arriving at a more securely based prognosis. I have had under observation a considerable number of women with systolic pressures of 270 who lived for many years. One, a member of my own family, who for over 30 years had a pressure of from 200 to 275, was nearly 100 years old at death.

Essential or primary hypertension is the most important type, being responsible for 15 per cent of all deaths after the age of 50 years.* It is the principal factor in what I have called *the failing heart of middle life*. The most striking objective result of essential hypertension is enlargement of the heart. At times one finds the heart enlarged in the absence of valvular disease and of concomitant hypertension. In the majority of such cases we may infer that a hypertension existed previously but had disappeared.

I shall not discuss in any detail the theories advanced in explanation of essential hypertension, because I should have to say after each one "not proved." A few points of interest may however be mentioned.

Hypertension is uncommon among the Chinese. Even foreigners living in China tend to have lower blood pressures (Foster [1]). Gunewardene [2] examined 200 Buddhist priests ranging in age from 30 to 80 years and found only one instance of real arterial hypertension. This striking difference between the oriental and the occidental has been attributed to differences in stature, muscular development, climate, habits of diet. But none of these nor all of them combined are sufficient to explain the difference. The greatest difference lies in their respective attitudes toward life. To the Buddhist priest the restlessness, the consuming ambition of the western business man are unknown and incomprehensible. He is never in a hurry,

* Cardiovascular disease, and in this hypertension is the chief factor, causes four times as many deaths as cancer.

never runs, not even as Gunewardene says, if his robes caught on fire. His only concern is life after death or some metaphysical problem. The placidity of the Chinaman is proverbial.

Foster thinks that in the Chinese the widespread use of watermelon seeds which apparently contain a substance that depresses blood pressure may be another factor in the lower vascular tension of the Chinese.

Of etiologic factors often not sufficiently appreciated I want to refer to two.

1. The possible influence of psychologic disturbances both in causing permanent hypertension and in producing temporary rises above the patient's habitual level. Disturbances in the sexual sphere, frustrations, etc., mental strain from business or domestic worries, unsatisfied ambition—seem to be capable of raising the vascular tonus.

2. Heredity. That heredity is an influential factor in hypertension is easily demonstrated, but that is merely a statistical fact which offers no fundamental explanation. We do not know what genes transmit the tendency or where the point of attack is on the blood vessels—on the vasomotor mechanism or on the musculature of the vessels, or back of both, on one or more of the hormone-secreting glands. The problems are endless.

It seems logical to place the immediate cause of hypertension in the arterioles, in the precapillaries. What is the nature of the process in the vessels? The variability, the labileness of the blood pressure in essential hypertension, the absence of structural, that is inflammatory or degenerative, changes in the arterioles in hypertensive persons dying in the early stages of their hypertension, suggest that spastic constriction of the arterioles in a large vascular bed such as the splanchnic area is the likely cause. For that reason I would make arteriolospastic and essential synonymous words.

Having carried essential hypertension back to the arterioles, to arteriolospasm, still leaves unanswered the question, what is the cause of the spasm. It is most probably chemical or hormonal in nature. It would, however, be an incomplete view of essential hypertension if we considered merely the angiospastic phase. The human system is an integration of innumerable quasi-independent mechanisms in harmonious relation, in homeostasis, to use Cannon's word, achieved by the self-steering of all the organs and tissues of body. If the neurovascular system shows evidence of disturbance as in hypertension, many fine adjustments are necessary to keep the body functioning. At any point in these interdigitating mechanisms a breakdown may occur. We are often unable to recognize the early signs of such a breakdown, one reason being that our thinking has hitherto been too anatomic and not enough physiologic. It is necessary to study many things. At one time the nervous control of the heart was considered the main element in cardiac contraction, until the myogenic theory gained preëminence. Perhaps we are at present giving too much prominence to the vasomotor mechanism and not enough to the intrinsic myogenic capacity for contraction and dilatation of the blood vessels.

Symptomatology. Essential hypertension may be symptomless for many years. It is often accidentally discovered during insurance or health examinations. As long as the heart is competent and able to counteract the resistance in front symptoms are minimal or absent.

The inaugural symptoms are mainly subjective—dizziness, headache, ringing in the ears, palpitation, slight dyspnea on effort, a sense of weight in the chest, nose bleed and irritability. Naturally these need not all be present. There may be only a single one in the beginning. The patient may ignore these symptoms or the unobservant doctor may overlook their cause, contenting himself with purely symptomatic treatment. Such patients eventually come under observation for more pronounced symptoms. These are most variable but are principally cardiac, cerebral or gastric.

The cardiac manifestations are those of early congestive failure—subjectively, dyspnea, objectively, peripheral edema, basal pulmonary congestion or unilateral hydrothorax. These, especially the latter two, must be looked for, otherwise they will be overlooked.

A rarer symptom, which might be called cardiopulmonary, is acute pulmonary edema, which has a tendency to recur at intervals and usually comes on at night. Air hunger, a sense of suffocation and fear of impending death, together with intense cyanosis, the physical signs of pulmonary edema, and at times but not constantly the expectoration of blood-tinged frothy fluid are the characteristic symptoms.

An attack of angina pectoris or of coronary occlusion may be either an early or a late symptom.

If the patient presenting such symptoms is carefully examined one or more of the following conditions will be found:

1. A high systolic and a relatively low diastolic pressure.
2. Cardiac enlargement.
3. Accentuated second aortic sound.
4. Often a systolic murmur at the aortic area.
5. In late stages a systolic murmur at the apex.
6. The radial vessels are usually soft but the temporal arteries are often tortuous.
7. Arcus senilis or annulus senilis.
8. There may be basal râles.
9. Hydrothorax, generally unilateral.
10. Edema of the shins and ankles.
11. Changes in the retinal vessels.

The electrocardiograph may show left axis deviation; in cases of long standing hypertension the degree of axis deviation may be marked, with prolongation of the QRS interval beyond the accepted top normal figure (0.1 second) due to increased conduction time through an hypertrophied ventricle. T_3 may be inverted and, according to Master, T_1 may also be inverted.

Many clinicians in speaking of the enlarged heart of hypertension use the term myocarditis. Strictly speaking this is not correct, for only rarely is there any evidence of inflammatory changes. Nevertheless, the heart muscle gives out. In order to get rid of the inappropriate term myocarditis, I have proposed myocardosis as a generic term to imply a functional rather than a structural change.

Cerebral Symptoms. These are extremely interesting and important for the understanding of the morbid physiology of hypertension. As a rule the disturbances are transient—hemiplegia, aphasia, monoplegia—and are usually ascribed to local angiospastic states. In severe cases generalized convulsions may occur which are often wrongly called uremic or epileptic. There may be no evidence of kidney damage and, setting in late in life, after fifty, they are not true epilepsy. Some speak of the condition as hypertensive encephalopathy; it is also called epilepsia tarda.[3]

During the convulsive seizure, and also in other types of encephalopathy before the onset of the particular symptom there is usually a sudden and abrupt rise in the systolic blood pressure, at times to 280 or even 300.

The focal symptoms mentioned above may last from a few minutes to 24 or 36 hours and may then subside without any residue. However, I have observed in numerous instances the persistence of one particular symptom, namely conjunctival anesthesia on the side that had been affected. I found this even in cases in which there was no anesthesia of the general body surface.

Besides angiospastic complications hypertension may lead to thrombosis and to rupture of cerebral vessels, i.e., to apoplexy, which is a frequent but by no means the most frequent mode of death in essential hypertension.

The gastric symptoms of hypertension are the gastric symptoms of the myocardial weakness, of the myocardosis, associated with and usually secondary to the hypertension. In the majority of instances the chief complaint is fullness and gaseous distention. Such a complaint by a person past 50 years who previously was free of digestive disturbances, is never to be treated lightly—it may mean the beginning of malignant disease or the failing heart of longstanding high blood pressure.

Diagnosis. It is important to make the diagnosis of essential hypertension in the early stages for the treatment will then be of most avail. A systolic blood pressure of 140 to 150 in an individual under 40 years is not to be ignored. Naturally it must be checked by several readings on different days so as to eliminate the factor of fear or excitement. A labile blood pressure showing wide swings from high to low is common in persons who later show a permanently elevated blood pressure.

The family history may be of significance. A history of hypertension, apoplexy, chronic heart or renal disease constitutes a background for hypertension in the descendants.

What shall be our criteria for the diagnosis of essential hypertension? As I view the subject these criteria are:

1. A persistently high systolic pressure.
2. A relatively low diastolic pressure.
3. Absence of disturbance of renal function.
4. Normal blood chemistry, that is as regards urea nitrogen and chlorides.
5. Absent or minimal eye changes.
6. A symptomatology trivial compared with the height of the systolic pressure.

At this point I might say something about prognosis, since due attention to that rather neglected phase of medical practice may help us in dealing with our patients. I shall be somewhat dogmatic as unconditional statements are more useful, provided they are favorable, in quieting the patient's mind.

1. An individual can live to be 80 or even 100 years with high systolic blood pressure.

2. Women bear high blood pressure better than men.

3. The diastolic blood pressure is more important as a prognostic index than the systolic blood pressure. A low diastolic blood pressure favors relative longevity.

4. Good renal function—traces only of albumin or no albumin, a few hyaline casts, good concentration—is a favorable prognostic finding.

5. Moderate cardiac hypertrophy is not unfavorable.

6. Cerebral accidents even of apparently trivial nature as well as anginal pain and retinal hemorrhages are all ominous signs.

Treatment. The treatment of essential hypertension is psychologic. By that I mean that it must be addressed to the intelligence rather than to the stomach of the patient. Such treatment ought to be part of our general scheme of preventive medicine in the sense that we should know the vascular characteristics, the tubing as Osler called it, of our patients and of their children. It certainly would give us valuable information if we were to examine the children of a man or woman in whom we had discovered high blood pressure—we might be able so to shape the lives of these persons as to guard them against hypertension in later life. To do all this means addressing ourselves to the minds of our patients and making them understand our aims.

We must assure our patients with essential hypertension of the comparative harmlessness of high blood pressure. To some extent we physicians have been responsible for making the laity blood-pressure-minded. A goodly number of patients have come to me all in a tremble saying, " Doctor, I've got blood pressure." When we can conscientiously do so we must relieve such persons of their anxiety.

Is it wise to tell the patient who has hypertension what his blood pressure is? Here the psychologic insight of the doctor and the general circumstances of the case must be the guide. My rule is this: If the patient is coöperative, then there is no need of his knowing his top figures. If he

is uncoöperative, then it may do good to tell him so as to scare him into good behavior.

Many hypertensive patients overwork, overeat, undersleep, and oversmoke. All these departures from the norm must be corrected. The man who takes to bed with him " the cares that infest the day " must be educated in a better habit. Attention must be given to the sexual life in both sexes—not that we can often help, but we can better understand. In some cases we can actually help—by advising infrequency of coitus when dealing with patients with superhypertension or with those approaching it.

Diet. Dietetics is the weakest subject in medicine. One can find authority for almost any conceivable diet for any human ailment. At one time it was customary in hypertension to give a salt-free, low-protein diet. However, excepting in those who indulge in meat and salt to excess, such extreme restriction was of no particular value in reducing blood pressure. All it did was to make the patient's life miserable. Moreover, Vilhjalmur Stefansson has shown that one might subsist on an exclusive meat diet for a year without any elevation of the blood pressure. Yet that might not apply to one who by heredity was destined to have high blood pressure; for such a one a low protein diet may be wise.

I think physicians are generally agreed that quantity is more important than quality, especially if the patient is overweight as is so commonly the case. We serve our patients best by teaching them moderation.

Alcohol has been under suspicion but in my opinion unjustly. It is true many free drinkers are hypertensive but such men as a rule are also free livers. A little whisky or a social glass of wine does no harm to the blood pressure.

With respect to tobacco, my opinion is quite different. I usually advise a minimal amount of smoking and if the patient has had cardiac pain I as a rule forbid tobacco altogether.

The bowels need attention. The patient should have a regular, easy, daily movement or two movements without straining. If need be, he should take a laxative, such as mineral oil or compound licorice powder. Toxic symptoms—occipital headache and mental depression—are sometimes quickly relieved by a colonic irrigation but this is not needed with any great frequency.

I have found in particularly constipated people that a weekly dose of castor oil is helpful.

Exposure to the hot sun should be avoided.

Exercise within reasonable limits is permissible. The trouble is to find the " reasonable limit." Wading in a swift stream to catch trout or salmon involves not only a severe physical but also an intense emotional strain—more than is good for a hypertensive fisherman. A prolonged golf game in the hot sun is likewise fraught with risk. Then there are persons, usually bankers or captains of industry, who are given to violent home gymnastics

—their habits must be studied and modified to suit their cardiovascular condition.

Medicinal Treatment. There is no specific drug in our pharmacopeia that will permanently lower arterial blood pressure. Many have been recommended, all have been found wanting. Their very number is proof of what I have said. I have used bismuth subnitrate, potassium sulphocyanate, and various organic extracts. They have all proved unreliable. Does that mean we are powerless in dealing with hypertension? By no means. The best results are obtained with sedatives, particularly those of the barbituric acid group. Phenobarbital in one form or another is very useful. The bromides are also helpful. One can combine them with advantage with elixir phenobarbital. I also like chloral hydrate which in reasonable doses is perfectly safe.

When the pressure is high and the heart begins to labor or convulsions occur or acute pulmonary edema, venesection often brings about immediate and dramatic relief.

In women at the menopause it is perhaps rational to try some of the endocrine products. If one takes the words of detail men or of the pharmaceutic literature as gospel, then these are sovereign remedies. We need to know a great deal more about them before any such statements can be made.

When the pressure is abnormally high, one may give the nitrites. I prefer for regular use erythrol tetranitrate in doses of 0.015–0.03 (¼ to ½ grain). In any emergency and when the patient has cardiac pain nitroglycerin under the tongue is the best remedy.

Roentgen-ray therapy has been used on the adrenals and on the pituitary gland, the latter on the theory that pituitary basophilism might be the cause of essential hypertension. The data are as yet insufficient for a definitive conclusion.

Physiotherapy, including diathermy, has been tried—personally, I have not seen much benefit from these measures.

Surgical Treatment. The general futility of medical treatment in established hypertension made the search for a surgical method altogether natural. A number of our bolder surgeons have devised procedures consisting in the main of cutting off the vasomotor supply to the abdominal arteries and arterioles. Theoretically this seems rational and can be attempted in various ways. It is not my present purpose to go into the history of this subject. Suffice it to say that the principal contributions are from the Mayo Clinic, from Adson and his coworkers, from the Crile Clinic, from Ann Arbor by Peet and his associates, and from the New York Hospital by Heuer and Page. One of the first attempts made to treat essential hypertension surgically was that of George Crile, who about 1910 performed a unilateral adrenalectomy. The operation was followed by a temporary fall in the blood pressure which later rose again to the preoperative level. This temporary success led Dr. Crile to add to the unilateral adrenalectomy

partial resection of the other gland. The blood pressure was affected somewhat more than by the unilateral adrenalectomy alone but it rose again to the disease level.

Crile next attempted to attack the function of the adrenal glands which he held responsible for the hypertension, by denervating the glands in two stages. This had a better effect, the improvement or cure lasting in some cases as long as five years. But recurrences were still common. He therefore extended the operation to include resection of the larger, minor and least splanchnic nerves; but even then results were not what had been expected, so that another approach was chosen, namely resection of the celiac ganglion and denervation of the aorta. The results in 25 instances, chiefly cases of malignant hypertension, have been most encouraging. The operation can be performed under nitrous-oxide-oxygen anesthesia.

Adson and his colleagues at the Mayo Clinic have employed two operative procedures:

1. Extensive bilateral section of the ventral roots of the lower thoracic and upper lumbar nerves.

2. Extensive subdiaphragmatic sympathectomy, which includes the splanchnic nerves on each side as well as the two upper lumbar ganglia and biopsy or partial resection of the suprarenal gland. It is still too soon to draw definitive conclusions as to the value of these operations but from observations to date Adson, Craig and Brown [4] prefer the subdiaphragmatic splanchnic resection with removal of the upper two lumbar ganglia and resection of the suprarenal gland.

Page and Heuer [5] in 17 patients performed section of the anterior nerve roots. They conclude that although the operation has markedly improved the clinical condition of many of the patients studied for periods up to 2½ years, its ultimate value in the treatment of hypertension has not been established. In their most recent article [6] they offer no encouragement.

From reading reports about surgical operations for the cure of hypertension and from my own very limited experience and from reports given to me by my surgical colleagues at the University Hospital, I would conclude that surgery as at present practiced has a long way to go before it justifies itself. But this does not preclude the possibility that some surgical method may be found that can be looked upon as curative. Perhaps we shall go through a stage similar to what occurred in the surgical treatment of hyperthyroidism. There was much criticism of the early operations. But that criticism has vanished before improved technic at operation and better pre- and postoperative care.

The pharmacologist, the biochemist, the clinician, must also continue their intensive studies in the hope of finding the chemical agent that causes vascular spasm. Perhaps the Banting of hypertension has been born.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE RELATION OF EMOTIONAL STRAIN TO ILLNESS*

By G. CANBY ROBINSON, *Baltimore, Maryland*

EMOTIONAL strain is an expression which is not readily described by words but is better appreciated by reference to personal experience and probably requires a measure of introspection for its understanding. However, emotional strain seems to be the best expression to describe the condition resulting from social or personal maladjustments which produce annoyance, tension or minor emotional disturbances over prolonged periods. Thackeray says in effect in " Vanity Fair " that it is not the great sorrows, but the little troubles that one daily has to bear that make life hard. It is the troubles that patients have to bear daily that cause emotional strain. It is often related to illness and becomes so closely integrated with it that emotional strain and illness are often inseparable and constitute two phases of a single problem, neither of which can be dealt with effectively alone.

For an appreciation and evaluation of emotional strain, consideration must be given to the personality and physical condition of the patient, the ideas, sensations and symptoms which he can express and describe, and the conditions of his environment, including his social status. Emotional strain is determined by the causes of emotions, the type of person in whom they are aroused and the character of the emotional reactions. This simple formulation is indeed superficial and does not bring into consideration psychopathological states or deep-seated psychic disturbances requiring even " minor " psychoanalysis for their disclosure. It is intended as a formula for the routine use of the practitioner of medicine, in order to reveal and evaluate the emotional components of almost every illness which brings the patient and doctor together.

It is well known by every intelligent person today, layman as well as physician, that many ailments are caused or modified by emotional strain, and many forms of treatment by various sorts of healers are successfully practiced on the basis of this knowledge. Although the private practice of medicine concerns itself, of necessity, with the emotional disturbances of patients, the organization and routine of the general hospital as operated today does not provide a large place for the study of the total individual and of the situations productive of psychogenic symptoms. Nor has it been practical to combine with the thorough and somewhat specialized form of medical education studies that lead to an understanding of the relation of

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personal and social problems of patients to their illness, except in psychiatric teaching.

Because of the foregoing considerations, an investigation of the nature and extent of emotional strain as related to illness has been undertaken in the Johns Hopkins Hospital, and measures for its relief, combined with the therapeutic regime prescribed for patients, have been employed. The study has been carried on with almost no attempt to select " suitable " cases, except that most of the patients have been those admitted to the wards and to the general dispensary of the medical service. Of the first 173 patients studied, in 83 or about half, emotional strain was found to form some part of the total clinical picture. In most of these patients organic disease existed and in some of them emotional strain played but a minor part, while in others it was the major factor in understanding the full meaning of the illness and in the treatment of the patient. This study has demonstrated clearly that emotional strain is of more importance as a component of illness in the usual run of hospital patients than had been suspected. The study was undertaken with the conviction that it would reveal certain so-called " accessory factors of health " which were not being considered as fully as might be desirable for the complete medical care of patients, even in a hospital where an unusually high standard of medicine is practiced and where there is a pervading interest in the patient as an individual.

The approach to the patients has been that of a clinician, and the study, diagnoses and treatment by the members of the hospital staff have first been carefully reviewed in order to have a clear conception of the physical status of the patients before the first interview. Patients have then been seen either on the wards or in the office adjoining the dispensary, and their personal and social histories have been expanded and their symptoms further analyzed in the light of the physical findings and laboratory studies.

Whenever any evidence of emotional strain has been revealed, the patients have been further studied in various ways, by home visits, interviews with other members of the family, the study of hospital records of other members of the family when they exist, inspection of working conditions, reports from social agencies and information from various other sources. In this work Miss Josephine C. Barbour, an experienced medical social worker, has been a valuable collaborator. This study is to be reported in detail subsequently.

It is the purpose of this paper to report a single case as an example of emotional strain as related to organic illness, to describe the method of its study and to discuss its significance in relation to treatment. The case is an illustration of how a rather simple social maladjustment may be relieved by a procedure requiring no special technical training and by the application of nothing more than the use of common sense after the cause of emotional strain is revealed.

Case Report

The patient, a 56-year-old white woman laundry worker, was referred to the general medical dispensary from Ophthalmology where she was under treatment for immature cataracts and an error of refraction. She was admitted on January 7, 1936 to the medical dispensary, where she has been studied and followed by Dr. A. Murray Fisher. She complained of poor vision and hoarseness. Her history at this time contained almost no other symptoms. She had lost three or four pounds in weight recently. The hoarseness had been present for nine years, and she attributed it to the atmosphere of the laundry. The history states that she had no headaches, dyspnea, precordial pain or swelling of her ankles, but had nocturia two or three times nightly. She said she did not feel nervous, but on a subsequent visit she said her work was quite hard and that she becomes excited and very nervous at times. She had had an attack of "pleurisy" 11 years previously, but had otherwise had good health.

On physical examination the patient was found to be a fairly well nourished blond woman weighing 118½ lbs., with a flushed face and a rather loud, husky voice, who appeared somewhat restless and emotional, with moist skin and a rather coarse tremor of the hands but no exophthalmos. The thyroid gland was palpable but not definitely enlarged or nodular. There was marked pulsation in the episternal notch, and the veins of the neck were engorged. Lungs were clear. Substernal dullness was somewhat widened but there was no cardiac enlargement. A systolic murmur in the aortic area and accentuation of the second aortic sound were noted, with a heart rate of 96. The systolic blood pressure was 210 and the diastolic 120 mm. Hg. The physical examination was otherwise negative. The Wassermann reaction was negative. The basal metabolic rate was plus 23, and a teleroentgenogram showed the heart shadows to be within normal limits, with moderate tortuosity of the aorta. There was a faint trace of albumin in the urine. The phenolsulphonephthalein excretion was 52 per cent in two hours and her hemoglobin was 92 per cent.

The basal metabolic rate was repeated twice at weekly intervals and determined as plus 29 and plus 45, the systolic blood pressure being 235 and the diastolic pressure 130 mm. Hg at the time of the first of these estimates, and 230 and 130 mm. Hg respectively at the time of the second.

A diagnosis of arteriosclerosis with arterial hypertension was made. The evident emotional tension, venous engorgement, marked hypertension and elevated basal metabolic rate led to the conclusion that the patient was threatened with cardiac failure, and a change of occupation and more rest were advised.

The patient was interviewed on February 27 and subsequently a visit to her home was made, the interview being undertaken as a routine measure in a process of sampling dispensary cases without selection because of any apparent problem. She was found to be an employee of the laundry of the Johns Hopkins Hospital where she had worked for nine years. During the past four years she had been quite nervous and emotionally disturbed, somewhat excited and had felt almost constantly "uncomfortable" while at work. Recently she had felt the strain of her work especially, and it now disturbed her so that she became excited and very nervous. During the past three months she had had shortness of breath on exertion, especially noticeable on walking up a moderate grade to her work, so that she had been obliged to go to work slowly and by a longer route which avoided the grade. She slept well, but was quite "unhappy" and had a sense of dread on going to work. She had no muscular fatigue, although she stood constantly while at work.

The personal history and social status of this patient indicated that she had experienced severe emotional disturbances in her past life, especially connected with her marital history. She had a satisfactory childhood as a member of a large family of seven children who were apparently quite congenial. Married at 21, her first husband was killed in a street accident about a year later, leaving her with an infant,

now a man of 34. She married again two years later, and soon began having difficulties, as her husband proved very unreliable and supported her for a number of years only on court order, leaving her and returning frequently, "as often as fifty times," she thinks. During this marriage two sons were born, now 31 and 28 years old. She was legally divorced seven years after this marriage, and five years later she contracted a third marriage which was also unsuccessful, ending in divorce without issue after about four years. The patient was 40 years old at this time, and at the age of 46 she began to work in the laundry of the Johns Hopkins Hospital, where she has been employed constantly for the past nine years.

The patient lives with one of her married sisters in a comfortable house of which she occupies the third floor. Her sister has been having "heart attacks" for a number of months, and suffers from shortness of breath and swelling of her ankles at times. Her brother-in-law is a pipe-fitter by trade, but has had no regular work for five years, and recently has been employed as a laborer on a W.P.A. project. He owns the house in which they live, but has been unable to pay his taxes for two years. The patient's three sons are unable to help her financially, as one has only part-time work, one is without a job while his wife works, and the third earns but little selling on commission. The patient is therefore entirely dependent on her own earnings.

The patient said that her work in the laundry went well until four years ago when she was promoted to be in charge of the flat ironing machines, with four girl helpers. The patient is unusually conscientious and tries hard to keep the work speeded-up, but is much annoyed by the young women who help her, as they are inattentive and "loaf on the job" when the forewoman is not in sight. The work has increased in volume in recent years, and she does not like it because of the "nervous strain." She said she noticed a complete change in her feelings when she was on a vacation during the summer of 1935, during which time she felt quite well.

From this history it was inferred that the vascular hypertension of the patient was probably related to the various emotional episodes of her married life, which had, we believe, made her especially susceptible to emotional strain. The severity of her hypertension indicated that she should be relieved of emotional strain as far as possible, and it was evident that tension and emotional disturbances were related to the conditions of her work.

In order to observe the patient's working conditions the assistant director of the hospital in charge of personnel was consulted, and a visit with him was made to the laundry. The patient was seen with her helpers, girls of 18 or 20 years who apparently had no particular interest in their work, which consisted in shaking out laundered clothes and placing them on the flat ironing machines. The work had to be kept up to a certain speed, in order to coördinate it with the other processes in the laundry, and the patient seemed to take the full responsibility for this. The superintendent of the laundry said that the patient had recently been failing in her work, as she did not have the necessary authority over her assistants, who teased and laughed at her. He said a change in her work would be helpful to the work of the laundry as well as to the patient. The superintendent agreed to change the work of the patient so that she no longer had the responsibility for other workers, although this could be done only with a reduction of wages of about $1.50 a week in fairness to other workers. The plan was then explained to the patient, the change being suggested as necessary for her health. After some hesitation and with some sense of disappointment, the patient agreed and her work was changed to sorting clothes on the other side of the flatwork ironing machines. This change was made on March 12, 1936.

The patient was seen on March 19, one week later, and said with enthusiasm that "a miracle has happened, and a big burden has been lifted from me." The feeling of excitement had gone, her neck, she said, no longer swelled and she was no

longer nervous or short of breath. Phenobarbital, prescribed one month previously, was discontinued by Dr. Fisher.

The patient has now been followed for over a year since her work adjustment and she has had no return of her previous symptoms. She continues to speak of the effects of the change as "a miracle" and has continued to work steadily, taking no drugs and no longer avoiding the up-grade walk to her work, as it now causes no shortness of breath. She has gained in weight up to 135 lbs. and gives the impression of being a contented, happy person. She no longer appears excited, her voice is not "husky," the face is not flushed and the neck veins are not engorged. Her basal metabolic rate was estimated at plus 20 in May, and plus 4 in December 1936.

The patient has been seen at monthly intervals or oftener, since January 1936 to May 24, 1937, and her blood pressure has been measured sitting up, lying down and after rest, with the object of finding its lowest level.

The blood pressure has shown no appreciable change throughout the period of observation, its lowest level having been 210 systolic and 120 diastolic, while on April 30, 1937 the systolic blood pressure was 245 and the diastolic 135 mm. Hg.

The point of special interest in this case is the almost sudden disappearance of her symptoms when she was relieved of an emotional strain, without any change in her elevated blood pressure. It was natural to attribute her symptoms as primarily caused by the somatic or organic disease from which she suffers, and the adjustment of the conditions of her work was undertaken with the idea that it might have a beneficial effect on her blood pressure. The effects of the work adjustment were, however, different from what was expected, but are instructive, as well as of much value to the patient.

There was a social maladjustment between the patient and the workers she was expected to control and direct. Her own conscientious spirit was in conflict with her young and inattentive assistants, and she did not have sufficient leadership to impose her authority upon them. As this situation had existed for four years with increasing lack of success and with changing assistants, the patient had been under a long emotional strain which had evidently been the main factor in the production of her symptoms. Mayo,[1] in his study of the human problems of an industrial civilization, shows the striking relation of proper social adjustment to the output of industrial workers, and our case suggests that the social adjustment of workers may have a definite relation also to their state of health.

It is interesting to note that among the changes which the patient reports is her ability to walk up the grade on her way to work without dyspnea, while for three months previous to her change of work, she felt forced by her dyspnea to avoid this grade. She also stated that she previously had a feeling of dread on going to work, which has disappeared. These statements are suggestive that the dyspnea was of psychogenic origin, and calls attention to the value of looking for psychic influences in the production of symptoms, even when there may seem to be a satisfactory explanation for them in the existing organic disease.

The change in the basal metabolic rate is also of interest, it having been as high as plus 45 in January 1936, and having been estimated as plus 4 in

December of the same year. The fall in the basal metabolic rate may have resulted from the ability of the patient to attain a more nearly basal state with the disappearance of excitement, or it may have had some other cause.

The relation of an elevated basal metabolic rate to emotion is familiar to all who have worked in this field, but its significance is not clear, although a number of investigations of this subject have been published.

Dunbar [2] has reviewed a number of these studies and says that the literature is inconclusive because the basal metabolic rate has not been usually correlated with the emotional state of patients but with certain disease groups. Landis [3] has studied the effect of emotions on the basal metabolic rate, and finds that an unpleasant emotion, produced by suggestion, is usually attended by a rise in the metabolic rate, and considers this rise as resulting from (a) increased supra-renal or thyroid (?) activity, or (b) increased metabolism of the central nervous system, or (c) increased muscular tonus and incomplete relation. His own experiments are not consistent, as changes in the basal metabolic rate were not always in the same direction or of the same magnitude with the same degree and kind of emotional disturbance. He concludes that changes in metabolic rate cannot be considered as a direct measure of emotional disturbances or cumulative emotional upset. DuBois [4] discusses the influence of emotion in elevating the basal metabolic rate, and gives some examples to illustrate it, but he offers no further explanation of the phenomenon.

It is evident that our present state of knowledge does not allow a definite interpretation of the change in the metabolic rate that occurred in our patient, but it is of interest to note that there was a well defined decline to a normal level from a distinct elevation with the disappearance of the subjective symptoms after the removal of emotional strain.

This patient is one of many in whom social and personal problems have been found to produce emotional disturbances leading to symptoms, either associated with or without outspoken organic lesions. This patient presented an unusually simple problem which was relatively easy to study and to solve, followed by such striking changes in symptoms as to leave no reasonable doubt as to the relation of cause and effect. The fact that the changes in symptoms occurred without any observable alteration in the outspoken vascular hypertension, indicates the value of studying patients with seemingly unalterable pathological conditions, from the point of view of emotional disturbances. They may be the major cause of distress and disability, and deserve the same careful attention that is given to the organic disease.

It is the daily experience of every practitioner of medicine to see patients whose symptoms are not adequately explained by the findings of the physical examination and laboratory study, especially if a rigid analysis of symptoms in relation to objective findings is made. When a patient presents definite evidence of disease the objective findings outweigh the symptoms of the

patient as the basis for diagnosis and treatment. Attention is focused on symptoms, however, when the objective findings reveal little evidence of disease or when they cannot be related to the complaints of the patient. Then the symptoms are usually recognized as of psychogenic origin. The tedious task of attempting to determine the psychogenic or emotional factors responsible for the symptoms is not usually fully carried out in hospital practice unless they seem of sufficient seriousness to call for a psychiatric consultation, or to lead to the transfer of the patient to the psychiatric service. In many hospitals these desirable procedures are impractical, even for patients with well-pronounced emotional disturbances, and in many cases, patients with symptoms of psychogenic origin are discharged from the wards with encouragement and reassurance, to be followed in the out-patient department or if already there, they are given sedatives, advice and at times referred to the medical social worker. These procedures are often beneficial, but too often the benefits are transient when the underlying causes of emotional strain remain uncovered and unconsidered in the plan of treatment, and patients continue to search for health by many visits to the dispensaries and by various types of special examinations and treatments.

The extent to which harmful emotions may be related to illness is strikingly shown by the extensive literature on the subject that has been collected and reviewed by Dunbar [2] in her book on "Emotions and Bodily Changes," in which it is indicated that emotional disturbances may affect practically every organ in the body and may play a part in many diseases. Cannon,[3] whose study of the physiological effects of emotions has continued throughout his many years of research, has recently expressed the opinion that the medical profession has not recognized in a practical way the nervous strain of modern life as a cause of disease, and he emphasizes the importance of regarding man as a "mind-body" unity. He discusses the ways in which success may be achieved in the treatment of emotional disorders by efforts to affect the emotions so that they are no longer harmful in the physiological sense, and will therefore cease to produce "tensions" and turmoil, responsible for many symptoms of illness causing distress and disability.

The study of the emotional components of illness presents many difficulties when an attempt is made to apply to patients the knowledge which the physiologists have developed, but in spite of this, it is the task of the physician to endeavor constantly to gain a better understanding of the effects of emotions in terms of established scientific facts. The case reported in this paper is offered as an example of how causes of emotional strain may be uncovered and removed without perhaps revealing the true, basic nature of its harmful action. Greater insight into these problems will come, however, as practitioners in various fields of medicine come closer in their attitudes and work with the psychiatrists, and when psychiatrists have more opportunity to study the emotional disturbances related to organic disease.

Meyer has for many years emphasized the psychobiological point of view as a field of science which should pervade medicine in all its phases, so that an understanding of the psychic aspects of illness may be progressively developed with the increase of experience and skill of the medical practitioner in any special field he may choose to cultivate. In speaking of the recognition and treatment of visceral and somatic symptoms which spring from mental causes, Meyer [4] says, " These disorders are common enough to make it a responsibility of any physician to learn something about the mental causes and their working. It is not likely that the general practitioner and the internist will be able to do their best without such knowledge. It will have to be acquired by a study of these events when and where they occur, with attention to the situation and to the facts that make reactions excessive."

It is surely true that emotional disturbances must be studied when and where they occur, and it cannot be foretold when or where they are to be encountered. For this reason constant watchfulness is needed by medical practitioners in every field, if emotional strain is to be given its proper evaluation in the production of the subjective evidence of illness, and in medical treatment. This attitude is difficult to maintain, in the wards and outpatient services of the modern hospital. This circumstance does not, however, diminish the importance of emotional strain in relation to illness, but should stimulate further efforts and new methods.

One of the foremost exponents of the study of the patient as an individual, among the internists in this country, who has given much thought and experimentation to the treatment of illness caused by emotional disturbances, is Dr. Joseph H. Pratt. It is hoped that what is written here may in some way be helpful to the cause in which he is much interested. As this paper is to be included in a volume dedicated to him as a Festschrift, it is especially gratifying to recall his encouragement and advice regarding the work of which this paper is a part.

Summary

A study of hospital patients with special reference to their social and personal problems has demonstrated that emotional strain frequently causes an important component of illness, deserving consideration in diagnosis and treatment.

A patient with an apparently unalterable organic disease is reported whose symptoms disappeared with the relief of emotional strain.

The significance of this case as an example of psychogenic symptoms in organic disease and the methods of study and treatment used are discussed.

The need of greater consideration of the patient as a total individual, in order to gain a better understanding of emotional disturbances as related to illness in hospital practice is emphasized.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE LIPID AND CHOLESTEROL CONTENT OF THE BLOOD OF PATIENTS WITH ANGINA PECTORIS AND ARTERIOSCLEROSIS *

By DAVID DAVIS, M.D., BEATRICE STERN, B.A., and GERSON LESNICK, M.D., *Boston, Massachusetts*

THE present study of the blood cholesterol and lipids in patients with angina pectoris of arteriosclerotic origin was prompted by the general interest in the relationship of cholesterol metabolism to the pathogenesis of arteriosclerosis. No systematic study of the cholesterol and lipid constituents of the blood in patients with coronary sclerosis is available in the literature.

There are, however, some studies on the cholesterol concentration in the blood of patients with arteriosclerosis. Bachmeister and Henes,[1] in 1913, after a study of 13 patients with arteriosclerosis and of nine normal individuals, stated that patients with atherosclerosis in the stage of development showed an increase in the blood cholesterol, but that no deviation from the normal was found when the process was stationary. The evidence presented was inconclusive. Weltmann,[2] without giving details, also reported increased values in 11 out of 12 patients with arteriosclerosis complicated by other diseases. It was his impression that hypercholesterolemia ran parallel, to a certain degree, with the severity of the arteriosclerosis. Denis,[3] in 1917, unconvinced because of the number and variety of conditions in which abnormal cholesterol values were reported, studied the cholesterol in 14 patients with atherosclerosis and compared their values with those of 20 normal individuals. The values of the normals varied from 167 mg. to 225 mg. per cent, and were essentially in agreement with Bloor's normal figures [4] for the same method. Five of the 14 patients with arteriosclerosis showed values of 250 mg. or above; these five patients had cardiac disease or nephritis. One of these had angina pectoris and a cholesterol value of 268 mg. Gorham and Meyers [5] also studied 10 patients with atherosclerosis and compared their values with those of 14 normal individuals. The values of the atherosclerotic group varied from 160 to 230 mg.; those of the 14 controls, from 130 to 190 mg. per cent.

In the reports mentioned, no careful consideration was given to the criteria employed in the selection of patients with arteriosclerosis. Mjassnikow [6] in 1926, presented more convincing evidence that he was dealing with arteriosclerosis. He used the following criteria: orthodiagraphic evi-

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From the Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston.

dence of enlargement of aorta in the absence of syphilis and hypertension, aortic murmurs, and clinical symptoms of coronary disease. He employed two colorimetric procedures [7, 8] and finding a constant difference between them recorded his values with one, the method of Grigaut. In 16 patients with arteriosclerosis, the blood cholesterol was elevated in every instance; 12 of these patients had angina pectoris. For control data he relied on the normal values for the method used and the results in his non-arteriosclerotic patients. These normal values varied from 120 to 170 mg.; those in the arteriosclerotic group, from 190 to 440 mg. In a second group of 25 patients in whom the diagnosis of arteriosclerosis was less certain, there were elevated values in 10 instances. Koulkov, Veiland and Tarnopolskaja [9] in 1931, studied cholesterol values in patients with cerebral arteriosclerosis, and noted increases in some instances. Their data, however, are too incomplete to permit proper evaluation.

Stepp [10] on the other hand, without offering evidence, stated that he was unable to find any abnormality of the blood cholesterol in patients with arteriosclerosis. Andes, Kampmeier, and Adams [11] came to a similar conclusion; these latter authors studied the blood cholesterol in 35 healthy medical students and compared values with those of 31 negroes, 16 of whom showed atherosclerosis. Of these 16, the ages in 11 varied from 20 to 30 years, and vascular disease was judged by compression of brachials, and in some instances, the condition of the dorsalis pedis. Elliot and Nuzum [12] in a study of the cholesterol values in hypertension incidentally estimated the degree of arteriosclerosis in their patients, by considering the condition of peripheral arteries, fluoroscopy of the aorta, and ophthalmoscopic examination of the fundi. In 19 patients with moderate or advanced arteriosclerosis, the blood cholesterol was essentially the same as in their controls.

In 1935, Duff [13] summed up the published data on the subject as follows: "It is sometimes stated that hypercholesterolemia is regularly associated with arteriosclerosis in man, but such statements are based on a literature much of which has no direct bearing on the question. Some publications which are frequently referred to in this connection have nothing to do with arteriosclerosis as such, but are concerned with various other diseases in which hypercholesterolemia is known to occur and with which arteriosclerosis may be associated. Whatever may be the truth of the matter, it is obvious that these data prove absolutely nothing regarding the occurrence of hypercholesterolemia in association with anatomic lesions of the arteries."

Recently, Landé and Sperry,[29] aware of the difficulty in recognizing arteriosclerosis clinically, attacked the problem by studying the blood lipids shortly after sudden death. The total cholesterol was then compared with the lipid content and the degree of gross atherosclerosis of the aorta. No correlation between the level of blood cholesterol and the degree of atherosclerosis was found. Many abnormal values due apparently to such factors as (1) infection during the few hours following the accident and (2) he-

molysis, were excluded, and reliance was placed on the constancy of the ratio of free to total cholesterol as a guide to the accuracy of values obtained. In a study of this kind, however, there are two possible sources of error that would not necessarily alter the free to total cholesterol ratio: (1) dilution of blood serum following hemorrhage (death in most instances followed automobile accidents), and (2) concentration of blood serum attending shock with loss of body fluids. Further, the range, 82 to 446 mg. per 100 c.c., of values obtained on these bloods drawn shortly after sudden death was greater than the distribution usually accepted as normal.

In the present study, attention was directed to the following considerations: (1) methods of analysis; (2) selection of patients with angina pectoris; (3) selection of control subjects; (4) statistical treatment of data.

Methods. There have been several recent criticisms of the colorimetric methods for the determination of blood cholesterol.[14, 15] For this reason the gravimetric method of Man and Peters [16] in addition to the colorimetric method of Meyers and Wardell [17] with apparatus for continuous extraction described by Ling [18] were used in this investigation. The values obtained by both cholesterol methods on the same blood were compared in 50 instances.[19] In general a fairly close agreement was noted. The average deviation of the colorimetric determinations from the gravimetric was plus or minus 8 per cent. Free cholesterol was precipitated with digitonin from the alcohol ether extract before saponification. The precipitates were weighed on a micro balance. Fatty acids and phospholipids were determined by the methods of Stoddard and Drury, and Fiske and Subbarow respectively, as modified by Man and Gildea.[20] The fatty acids were determined as milli-equivalents and translated into milligrams by multiplying by 277, the average molecular weight of the fatty acids as they usually occur in blood. Measurements were made in duplicate. Venous blood was drawn with minimum stasis from patients in the post-absorptive state. The basal metabolic rate was determined in duplicate with the Collins, Benedict-Roth apparatus and results calculated according to the Aub-DuBois [21] standards.

Selection of Subjects. A large group of patients with angina pectoris and coronary disease was available in this clinic. Most of these patients were followed by Drs. Riseman and Brown and the diagnoses of angina pectoris were confirmed by exercise tolerance tests.[22] The duration of the disease, in every patient on whom lipoid studies were made, was more than one year. Approximately one-third of the group gave a history consistent with cardiac infarction in the past. Patients with rheumatic and syphilitic heart disease were excluded. All were ambulatory, and at the time blood samples were taken, they were not suffering from any of the usual cardiac complications, such as acute coronary thrombosis, or circulatory failure. Those selected for this study were likewise free from other complications that might alter the lipoid metabolism, such as myxedema, diabetes, or

nephritis. There had been no departure from their usual diets, and no obvious changes in weight. The majority of patients had been on some form of medication such as aminophyllin or small doses of nitroglycerine. Ten of the 59 patients studied were female. The ages in the entire group varied from 38 to 69 with a mean of 55 years.

Selection of Controls. The selection of controls presented a problem. To insure a low incidence of atheromatosis, one would naturally choose very young adults. On the other hand such a selection might be held unsatisfactory because of the possibility of lipid and cholesterol values increasing with age. It has been shown, however, that the distribution of the lipoid values in older individuals is the same as in young adults.[23] Our controls were healthy individuals chosen from among the students, physicians, and workers of the hospital. Subjects in both lower and upper age groups were included. The ages in this group of 54 subjects varied from 18 to 69 with an average of 34 years. In 28 of these in whom more complete blood lipid studies were made, the average age was 42 and 14 of these were above the age of forty-five.

Results

Total Blood Cholesterol. The cholesterol values by the colorimetric method in 59 patients with angina, and in 54 normal controls are shown in table 1. More values in the higher range are noted in the angina group. Thirty-five patients, as against 16 in the control group, showed values above 250 mg. The highest cholesterol in the control group was 287 mg. while in the angina group there were 13 patients with values above 287 mg. Figure 1 shows the distribution of these values expressed in per cent of total cases. The values obtained in patients with angina pectoris are seen to taper off slowly with a spread considerably beyond the control values. The mean for the angina patients is 260 mg. $\pm$ 6.9; the mean for the control group 218 mg. $\pm$ 5.4; the difference 42.0 mg. $\pm$ 8.8. (Table 3.)

Table 2 gives the cholesterol values by the gravimetric method in 32 patients with angina pectoris and in 22 controls. More of the values in the angina group, as measured by this method, are also in the higher range. Eighteen of 32 values in patients with angina, or 56 per cent, were above 250 mg. while in the normal group only five or 22 per cent of 22 values were above 250 mg. There were 12 values in the anginal group above 282 mg., the highest normal cholesterol. The distribution of these values is shown in figure 2. The mean cholesterol for the angina group is 259 mg. $\pm$ 10.2; the mean for the control group 219 $\pm$ 8.7; the difference, 40 $\pm$ 16.7. (Table 4.)

Free Cholesterol. A comparison of the values for free cholesterol in 31 patients with angina and 16 normal controls (table 2) shows again a higher average value for the former. Twenty-one of the 31 values were 80 mg. or above, as against five out of 16 normal controls above 80 mg.

TABLE I

A Comparison of the Fasting Blood Cholesterol* in Patients with Angina Pectoris and in Normals

Angina Pectoris					Normals				
Case No.	Age	Sex	B.M.R. % deviation from the normal	Cholesterol mg./100 c.c.	Case No.	Age	Sex	B.M.R. % deviation from the normal	Cholesterol mg./100 c.c.
1	57	M.	−7	119	1	54	M.		131
2	66	M.	+11	184	2	26	F.	+12	145
3	57	F.	−10	185	3	53	M.		150
4	57	M.	−10	190	4	52	M.		157
5	57	M.	−24	192	5	30	F.	−12	160
6	47	F.	+2	195	6	20	F.	−16	166
7	55	M.	+2	200	7	68	M.		172
8	50	M.		204	8	25	M.	−11	173
9	59	M.	−8	205	9	22	M.		173
10	57	M.	−4	211	10	24	M.		178
11	51	M.	+3	213	11	25	F.	−25	180
12	56	F.	−2	215	12	49	M.		186
13	57	M.	−6	217	13	60	M.		190
14	54	M.	−14	218	14	33	M.	+5	192
15	69	M.	−1	222	15	24	M.	−15	193
16	59	M.	−2	223	16	22	F.	+2	195
17	58	M.	+7	224	17	24	F.	−13	197
18	60	M.	−20	232	18	22	F.	−19	197
19	54	M.	−17	236	19	29	M.		203
20	53	M.	−15	240	20	26	F.	−9	204
21	38	F.	+1	243	21	25	M.	−12	204
22	58	M.	−2	244	22	22	M.	−6	206
23	58	M.	−21	246	23	53	M.		207
24	60	M.	+6	249	24	20	F.	−12	208
25	48	M.	−14	251	25	18	F.	+1	208
26	54	M.	−12	254	26	48	M.		209
27	41	M.	−19	255	27	28	M.	−23	210
28	51	M.		256	28	22	M.	−6	214
29	41	M.		258	29	22	F.	−5	216
30	58	M.	+14	258	30	48	M.		220
31	55	M.	−5	262	31	28	M.		225
32	63	M.	+6	266	32	48	M.		236
33	60	M.	−10	266	33	30	M.		236
34		F.	−16	267	34	38	M.	−35	237
35	61	M.		267	35	25	M.	−16	238
36	57	M.	−20	267	36	26	M.	−17	238
37	60	M.	−20	268	37	26	M.	−27	244
38	52	F.	+3	269	38	62	M.		246
39	54	M.	+7	270	39	26	M.	−4	251
40	55	M.	−13	273	40	50	M.		251
41	55	M.	−23	278	41	25	M.	−15	252
42	58	M.	−5	279	42	25	F.	−4	252
43	50	M.	−21	279	43	34	M.	−23	253
44	67	M.	−4	281	44	55	M.		254
45	50	M.	+4	282	45	49	F.		254
46			−27	283	46	41	M.		256
47	56	M.	−22	289	47	38	M.		264
48	58	F.	−23	298	48	54	M.		270
49	60	M.		303	49	30	M.	−21	273
50	50	F.	−19	305	50	26	M.	−15	275
51	53	M.	−12	308	51	26	M.	−6	279
52	52	M.		312	52	27	M.	−20	286
53	56	F.	−1	329	53	25	M.	−28	286
54	59	M.	+11	333	54	33	F.	−21	287
55	38	M.	−13	350					
56	54	F.	−6	362					
57	54	M.		368					
58	57	M.	−15	380					
59	48	M.	−4	413					

* Cholesterols done by colorimetric method (Meyers, Wardell, Ling).

FIG.

FIG.

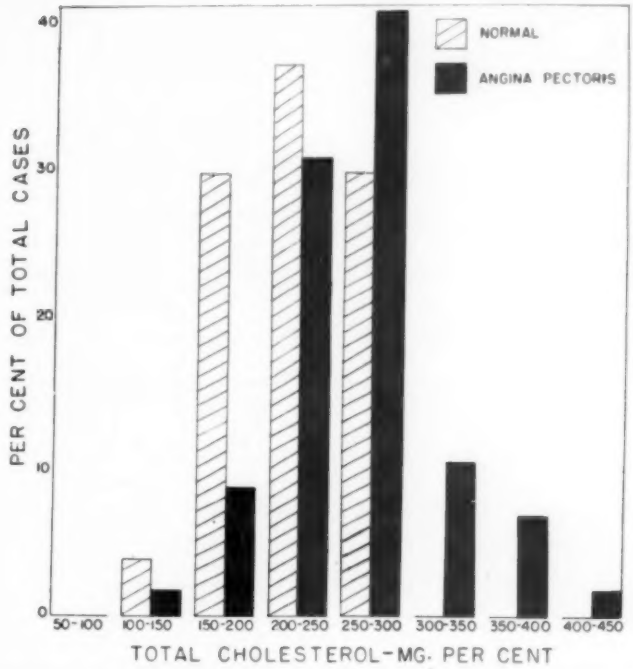

FIG. 1. Distribution of total cholesterol in 59 angina pectoris patients and 54 normals. Method of Meyers, Wardell, Ling.[28]

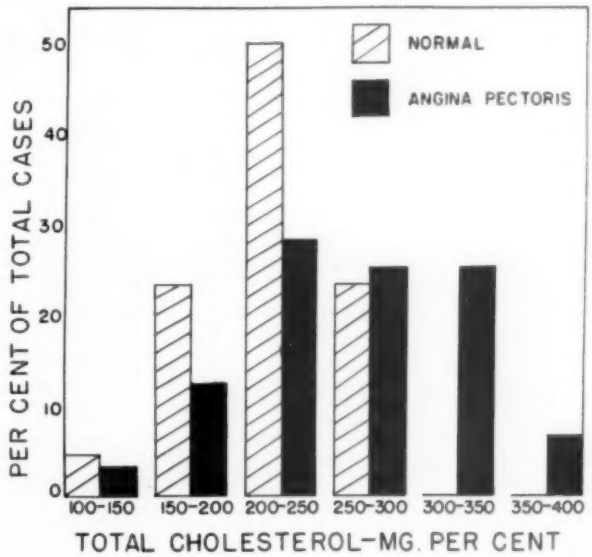

FIG. 2. Distribution of total cholesterol in 32 angina pectoris patients and 22 normals. Method of Man and Peters.[26]

TABLE II

A Comparison of the Fasting Cholesterol and Blood Lipoids in Patients with Angina Pectoris and in Normals

Angina Pectoris									Normals							
Case No.	Age	Sex	Type	Hypertension	Lipoid Phosphorus mg./100 c.c.	Fatty Acids mg./100 c.c.	Cholesterol		Case No.	Age	Sex	Type	Lipoid Phosphorus mg./100 c.c.	Fatty Acids mg./100 c.c.	Cholesterol	
							Free mg./100 c.c.	Total mg./100 c.c.							Free mg./100 c.c.	Total mg./100 c.c.
1	56	M.	I	+		415			1	68	M.	L	8.3	268	48*	173*
					10.0	444		222*	2	47	M.	P	8.1	380		
					10.9	372	83	278	3	52	M.	L	9.3	308		
2	60	M.	I	+		420			4	60	M.	P	8.2	252		171
					10.2	456			5	41	M.	I	11.0	494	74	234
					9.4	359	76	230	6	35	M.	I	9.3	468		221
3	58	M.	P	0		436			7	33	M.	L	8.6	281		
					10.8	454			8	30	M.	I	10.1	450	64	194
					13.9	466*	91	290*	9	22	M.	L	7.1	243		
					10.7	417	87	304	10	24	M.	L	5.1	134	38	101
4	59	M.	P	0		570			11	53	M.		9.8	398		
						502			12	53	M.	L	9.0	302	68	257
5	53	M.	I	0	10.9	450	85	270	13	23	M.	P	7.7	279	67	206
6	48	M.	P	++		617			14	49	F.	L	9.8	378	67	202
					15.4	594		355	15	53	M.	P	8.0	345		212
7	59	M.	I	0	10.2	450	80	257	16	62	M.	I	9.8	463	82	238
8	63	M.	I	+	10.7	462	90*	304	17	54	M.	P	10.4	444		
9	56	M.	I	0	10.8	464	82	264	18	53	M.	P	9.3	414		194*
10	60	M.	I	+	11.3	560	65	178	19	55	M.	I	11.9	522	71*	248
11	54	M.	I	++	11.4	345	76	239	20	46	M.	P	7.6	457		238*
12	55	M.	I	0	11.1	392	93	300	21	52	M.	P	10.9	516		239*
13	59	M.	I	0	11.2	428	103	300	22	36	M.	I	11.4	480	88	270
14	46	F.			10.0	416	71	210	23	29	M.	I	8.6	345	66	178
15	50	M.	L	0		392	95	296	24	27	M.	P	10.8	359	83	267
					12.8	420			25	38	M.	I	8.6	401	89	258

TABLE II—*Continued*

Angina Pectoris									Normals								
Case No.	Age	Sex	Type	Hyper-tension	Lipoid Phosphorus mg./100 c.c.	Fatty Acids mg./100 c.c.	Cholesterol		Case No.	Age	Sex	Type	Lipoid Phosphorus mg./100 c.c.	Fatty Acids mg./100 c.c.	Cholesterol	
							Free mg./100 c.c.	Total mg./100 c.c.							Free mg./100 c.c.	Total mg./100 c.c.
16	58	M.	P	0	11.1	416	85	281	26	23	M.	L	10.2	278	69	218
17	66	M.	I	0	10.3	304		110	27	39	M.	P	12.2	328	64	215
18	66	M.	I	0	16.6		114	260	28	29	M.	P	11.4	349	86	282
					10.5	662										
19	51	M.		+	13.9	441	76	208								
					8.1	393	73	150								
20	51	M.	P	0	8.5	352	66	181								
21	58	M.	P	0	11.0	422										
22	54	M.	I	0	9.6	410	89	220								
23	55	M.	P	0	8.6	380										
					8.7	277	70	242								
24	41	M.	L	0	10.5	438	85	243*								
25	69	M.	L	++	10.4	440	74	219								
26	56	F.	P	+	10.2	483	84									
					11.6	347	80	236*								
27	51	M.	P	0	12.5	548	97									
28	55	M.	P	+++	12.5	435	105	303								
29	61	M.	L	0	12.0	380	88	312								
30	54	F.	I	+	14.9	487	115	340								
31		M.	I	0	9.9	238	70	184								
32	67	M.	I	+	11.4	409	95	321								
33	38	M.	L	0	12.6	409	114	350								
34	52	M.	P	0	11.4	370	97	328								
35	50	M.	P	0	8.9	366	69	220								

* Analysis not in duplicate.
P Pyknic
L Leptosome
I Intermediary

Hypertension: none—0
slight—+
moderate—++
marked—+++

There were no values in the control group above 89 mg. while in the anginal group there were 13 values above 89 mg. The comparative distribution is seen in figure 3. The mean for the control group is 70.2 mg. $\pm$ 3.5; the mean of the anginal group is 86.4 mg. $\pm$ 2.5; the difference 16.2 $\pm$ 4.3. (Table 3.)

Phospholipids. Table 3 shows the distribution of the phospholipids as milligrams lipid phosphorus in 34 patients with angina and in 28 normal controls. Twenty-six of 34 values in angina were above 10.0 mg. while but 10 of the 28 control values were above 10.0 mg. The highest normal value was 12.2 mg. while in the angina group there were seven values above 12.2 mg. Figure 4 shows the distribution of these values; the differences are obviously significant. The means for the anginal and control group are 11.2 mg. $\pm$ 0.26, and 9.4 $\pm$ 0.30 respectively, with a difference of 1.77 $\pm$ 0.40. (Table 3.)

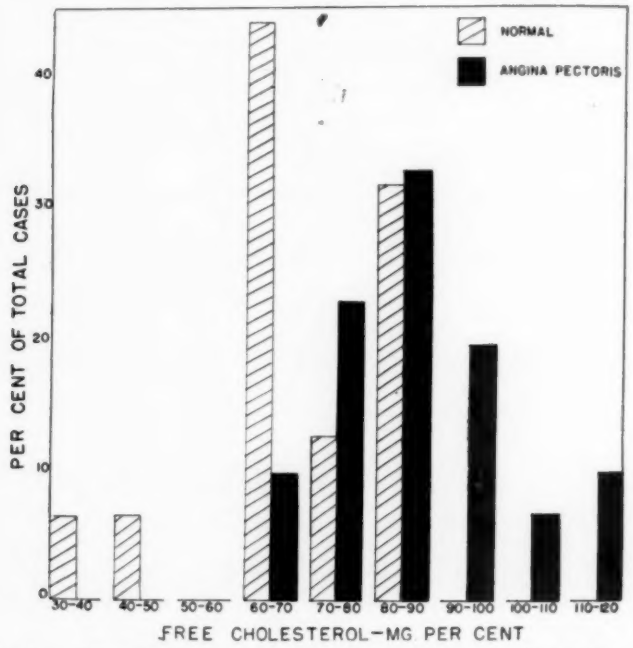

FIG. 3. Distribution of free cholesterol in 31 patients with angina pectoris and 16 normals.

Fatty Acids. A comparison of the fatty acid values in 35 patients with angina, and in 28 normal controls is shown in table 3. Figure 5 shows a tendency toward higher values in the patients with angina for this lipid also. The differences are not so marked as in the case of cholesterol and phospholipids. The mean for the normal fatty acids is 369 mg. $\pm$ 18.1; for the anginal group, 429 mg. $\pm$ 13.7, the difference 60 $\pm$ 22.7.

Summary of Statistical Analysis of Data. In table 3 the values of the several lipid constituents of the blood of patients with angina are com-

TABLE III

Summary of Statistical Analysis of Data*

	M mg. per cent	S	S_m	D	S_d	D/S_d	P
Total cholesterol colorimetric							
Normal	218	39.8	5.4				
Angina pectoris	260	53.2	6.9	42.0	8.8	4.8	.001
Total cholesterol gravimetric							
Normal	219	40.6	8.7				
Angina pectoris	259	57.5	10.2	40.0	16.7	2.4	1.6
Free cholesterol							
Normal	70.2	13.9	3.5				
Angina pectoris	86.4	14.1	2.5	16.2	4.3	3.8	.015
Fatty acids							
Normal	369	95.5	18.1				
Angina pectoris	429	81.3	13.7	60.0	22.7	2.6	1.6
Lipoid phosphorus							
Normal	9.4	1.61	0.30				
Angina pectoris	11.2	1.52	0.26	1.77	0.4	4.5	.002

* When two or more measurements were made in a given patient, the average value was utilized in computation.

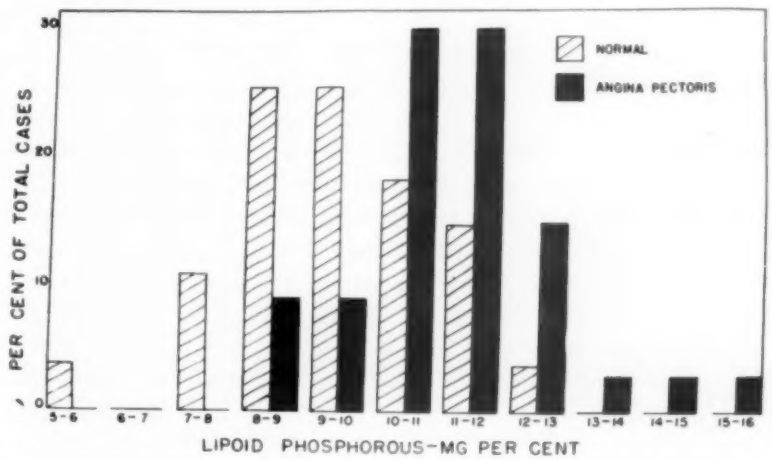

FIG. 4. Distribution of lipoid phosphorus in 34 angina pectoris patients and 28 normals.

pared with the values in the normal control group. The column M gives the arithmetic mean of the determined values. The column S gives the standard deviation of the series calculated according to the formula $S = \sqrt{\Sigma D^2/N - 1}$ where ΣD^2 is the sum of the squares of the differences of the individual values from the mean value and N is the number of cases. The column S_m gives the standard deviation of the mean and is equal to $S/\sqrt{N}$ or $\sqrt{\Sigma D^2/N(N-1)}$. The column D gives the difference between the mean of the angina group and the normal group. The column S_d gives the standard deviation of that difference which is equal to the square root of the sum of the squares of the standard deviations of the

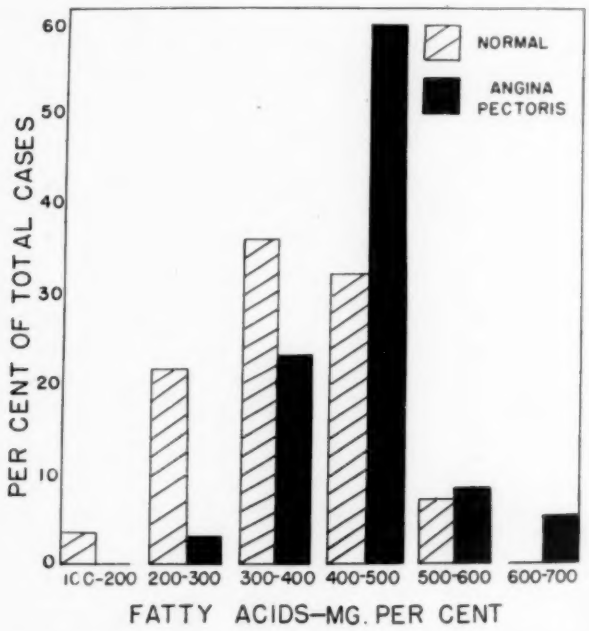

FIG. 5. Distribution of fatty acids in 35 angina pectoris patients and 28 normals.

respective two means. The column D/S_d gives the ratio of the difference to its standard deviation. In general, values of the ratio above two are considered probably significant and values above three practically certainly significant. Column P gives the probability of a difference as great or greater than the one listed, being due purely to chance. A value of P of 1.0 indicates a probability of 1 per cent or one chance in 100 of the difference being due to a sampling error.

The Normal Values. Man and Gildea [24] recently studied the blood lipid values in a group of normals. In 76 healthy individuals the mean of the cholesterol values was 196.8 ± 4.0, 22.1 mg. lower than the mean in our control series. This difference is probably significant. Their phospholipid

values were close to ours with D/S_d less than one, although our values were 3 to 5 per cent higher.

Gildea, Kahn, and Man [25] make the interesting observation that in males the normal lipid values are higher in those with a pyknic and lower in those with a leptosome type of constitution. The pyknic type refers to the stocky individual of short or middle height, rounded figure, broad face and large rounded head on a short massive neck; the leptosome or asthenic, to those with opposite attributes such as greater development of extremities, narrower trunk, longer neck and oval face. The incidence of pyknic types in our small group of 22 normals was slightly higher than in their normals. The proportion of Jews was small in their normals, whereas in our series they comprised half. The cholesterol values of 13 of these Russian-Jewish normals gave an average of 235 mg.; the average of nine Gentiles was 193 mg. Eliminating one value of 101 mg. in the latter group, which was extremely low, the average was 212 mg. The ratio of the difference between the two means of Jew and Gentile (with the low value of 101 eliminated from the Gentile group) to its standard deviation is 1.69. The probability of such a deviation being due purely to chance is 9.1 out of 100. The phospholipid difference in 14 Jews and 11 Gentiles was similar. $D/S_D = 1.74$, and the same was true of the fatty acids to a lesser degree, $D/S_D = 1.43$. These differences raise the possibility of differences due to race. In the group, however, of 59 patients with angina and 54 normal controls which we studied by the Meyers and Wardell method there were three and 14 Gentile subjects respectively. Racial influence, if it exists, was therefore unimportant in our comparisons.

It will be noted that the controls include subjects in both the lower and upper age groups. It has been shown by Page, Kirk, Lewis, Thompson, and Van Slyke [23] that blood lipids and cholesterol values of individuals in different age groups are essentially the same. Our data, as far as they go, are in conformity with this important finding. For example, the average cholesterol of 27 normal individuals below the age of 30 is 215 mg. (table 1) as compared with an average of 218 mg. for the entire group of fifty-four. Also in nine normals above the age of 50 (table 2) the mean cholesterol measured by the gravimetric method was 214 mg. as compared with 219 mg. for the entire group of twenty-two. It is of further interest in this connection that measurements made in a few normal subjects at intervals over a period of approximately three years reveal an individual tendency to maintain a rather constant general level of blood cholesterol.

The Inter-relationship of Lipid Fractions; the Ratio of Free to Total Cholesterol. The inter-relationship of the lipid constituents can be seen in table 2. Although there are a number of exceptions, the lipid fractions in the same individual, either normal or angina pectoris, are in a general way proportional to each other. The cholesterol and phospholipid values are more closely proportionate to each other than either of these to the

fatty acid values. A similar proportionality was found in well treated diabetic patients by Man and Peters [16] and in malnutrition by Man and Gildea.[30] The parallelism of cholesterol and phospholipid values in their series was closer than in ours.

The ratio of free to total cholesterol (figure 6) appeared to be fairly constant for both the normal and the angina groups with a free cholesterol value ranging from 27 to 44 per cent of the total. The mean of the free cholesterol percentages of the totals in the normal group is 32.3 per cent, in the angina group 33.4 per cent. These findings agree fairly closely with those of Page, Kirk, Lewis, Thompson, and Van Slyke [23] who found in normals that the mean of the free to total cholesterol ratios was approximately 37 per cent. In a recent study of 91 healthy adults, Sperry [26] using his own method found an average ratio of 26.9 per cent with a maximum of 30.1 per cent and a minimum of 24.3 per cent.

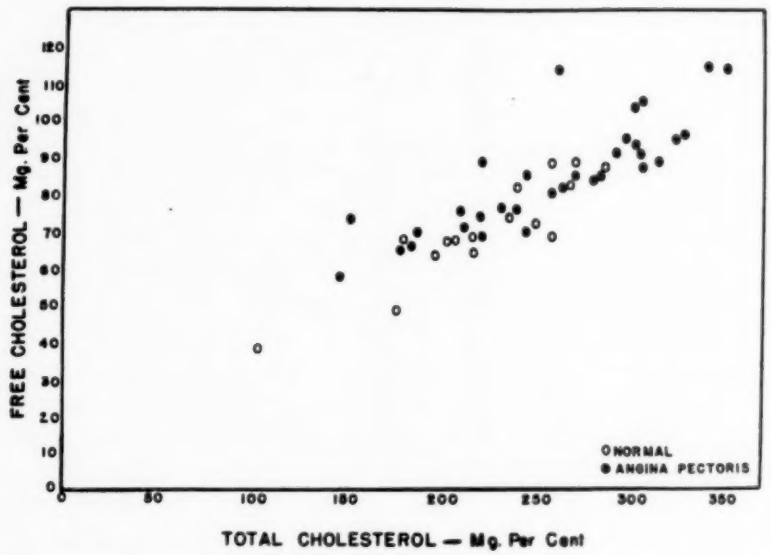

FIG. 6. The ratio of free to total cholesterol in 32 patients with angina pectoris and in 16 normal controls.

Relation to Basal Metabolic Rate and Hypertension. To rule out any possible influence of a preponderance of low metabolic rates in one group or another, the average metabolic rates were considered (table 1). The average basal metabolic rate for 52 patients with angina was minus 8 per cent, for 32 controls minus 13 per cent. The higher incidence of basal metabolic rate values of minus 20 per cent or below in both groups is noteworthy in the absence of clinical hypothyroidism.

In table 2, the presence and degree of hypertension in the patients with angina pectoris are recorded. One plus represents a systolic pressure of 160

to 180 mm. or a diastolic of 95 to 100 mm.; two plus, a systolic of 180 to 200 mm., or a diastolic of 100 to 110 mm.; and three plus, a systolic above 200 or a diastolic above 110 mm. of mercury. It will be observed that only four of 34 patients showed moderate or marked hypertension (table 2). Hypertension, generally mild, was present in 13 patients or in 38 per cent. The average cholesterol and phospholipid values of these 13 patients were 266 mg. and 11.6 mg. respectively. The average cholesterols of 18 and the average phospholipids of 20 patients, both groups without hypertension, were 251 and 10.8 mg. respectively. It is obvious that these slight differences are not significant and that the elevated values obtained were not related to hypertension.

Discussion

An analysis of the data presented indicates that the blood lipids are frequently elevated in patients with angina pectoris of atherosclerotic origin. Increases were noted in all the lipid fractions: cholesterol, free and total, lipid phosphorus and fatty acids. These increases are probably more significant than is apparent, in view of the fact that an appreciable percentage of normals have or will develop coronary atherosclerosis. The differences noted obviously applied only to groups. As evidenced in figures 1 to 5, there was considerable overlapping of the values in the patients with angina and those in the control group. It is apparent that lipid values are normal in a large group of patients with angina pectoris. The occurrence of definitely elevated values in some, however, suggests that the lipid and cholesterol metabolism is disturbed either primarily or secondarily in at least a certain group of patients with angina pectoris.

When rheumatic and syphilitic heart diseases are excluded, angina pectoris is, in the majority of instances, associated with coronary atherosclerosis. Stocks [27] states, for example, that a reasonable and conservative estimate of the incidence of atherosclerosis of the coronary arteries in patients with angina pectoris is 85 per cent. To obtain further data on this question an analysis was made of 36 necropsy protocols where angina pectoris of arteriosclerotic origin was the clinical diagnosis. Thirty-two or 89 per cent of these patients showed a moderate or marked degree of atherosclerosis of the coronary arteries.

Although there are notable exceptions, coronary atherosclerosis is usually associated with generalized changes of the same kind in the aorta and other vessels of the body. Saphir, Priest, Hamburger, and Katz,[28] for example, found moderate or severe general arteriosclerosis in every one of a group of 34 patients with coronary arteriosclerosis and infarction. This would imply that the lipid findings in angina pectoris are in some measure true for general arteriosclerosis.

Conclusion

The average cholesterol, free and total, lipid phosphorus and fatty acids of a group of patients with angina pectoris of atherosclerotic origin were found higher than in a group of control subjects. There was considerable overlapping with the values of many angina patients in the normal range. A small group with angina pectoris showed values well above the highest normal value.

We wish to thank Marie C. Volk and Edward S. Glasser for their technical assistance in this investigation.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE SIGNIFICANCE OF CARDIAC ENLARGEMENT CAUSED BY ARTERIOVENOUS FISTULA *

By WILLIAM B. PORTER, M.D., F.A.C.P., and JAMES P. BAKER, JR., M.D.,
Richmond, Virginia

FOLLOWING the establishment of a fistulous connection between an artery and a vein, there occur changes in the dynamics of the circulation which result in varying degrees of cardiac enlargement and of dilatation of the involved artery and vein proximal to the fistula. The extent of the changes depends mainly upon the size of the vessels involved and the caliber of the fistula.[1]

In 1924 Holman [1, f] expressed the opinion that the dilatation of the proximal artery and vein was an adjustment mechanism for the accommodation of the increased volume of blood flowing through the artery-vein fistulous system. These conclusions are tenable and universally accepted. The causation and the significance of the cardiac enlargement which occurs in association with the vascular changes remained a debatable problem.

From a series of 11 cases of acquired arteriovenous fistula four have been selected for special study because we felt they offered opportunities for the acquisition of fundamental data relevant to the significance of the cardiac enlargement.

1. In three instances the femoral vein and artery were involved at approximately the same anatomical point. The popliteal was involved in the fourth.

2. In one instance the fistula had existed for five weeks, in another eight months, in the third three years and seven months, and in the fourth 21 years.

3. The location of the fistulae made it possible to study the venous pressure and the velocity of venous flow proximal to the fistulous connection.

METHODS USED

All physiologic studies were made three to four hours after the last meal, the patient remaining in bed on these days. The venous pressure was measured by direct venipuncture, using the apparatus and technic of Moritz and von Tabora.[2] Measurements of the velocity of blood flow were made with the use of the cyanide method of Robb and Weiss.[3]

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From the Department of Medicine, Medical College of Virginia, Richmond, Virginia.

The operations were done by Dr. I. A. Bigger, Chief of the Surgical Staff, Hospital Division, Medical College of Virginia, Richmond, Virginia.

The heart size was determined by the use of teleroentgenograms. These were standardized to constant chest diameters and the position of the diaphragmatic level. The prediction formula of Hodges and Eyster [4] was used in calculating normal transverse cardiac diameter.

Case Reports

Case 1. S. B., a negro laborer, aged 45, five weeks previously had received a bullet wound in the upper right thigh. He stated that he was working as a laborer 10 days after the accident without subjective complaints or impaired function of the involved limb.

Physical examination: A well developed negro man in a normal state of physical fitness. The local phenomena of an arteriovenous fistula were present at the apex of Scarpa's triangle on the right side, indicating a fistulous connection between the right femoral artery and vein.

	Fistula opened	Fistula closed
Blood pressure	systolic 130, diastolic 65	systolic 150, diastolic 100
Pulse rate	79 per minute	62 per minute
Vital lung capacity: predicted normal	5,360 c.c.	
actual	5,180 c.c.	

Electrocardiogram: normal, no change following operation. The physiological studies and heart size data before and after operation are shown in figure 1.

Case 2. A. H., a white farmer, aged 32, had received a bullet wound in the upper left thigh three years and seven months previously. He stated that he resumed his farm work two weeks after the accident. He noticed a thrill and swelling over the femoral area a few days after receiving the wound. For the past seven months there had been some swelling of the left foot and ankle. During cold weather this foot became numb and there was aching in the calf muscles of the left leg if he walked rapidly up grade. The subjective complaints were not sufficient to stop him from his work. He came for relief of the functional impairment and swelling in the left leg.

Physical examination: A well developed man in a normal state of physical fitness. The local phenomena of an arteriovenous fistula were present 2 cm. below the apex of Scarpa's triangle on the left side indicating a fistulous connection between the left femoral artery and vein. There was slight pitting edema of the left ankle.

	Fistula opened	Fistula closed
Blood pressure	systolic 130, diastolic 55	systolic 140, diastolic 95
Pulse rate	88 per minute	60 per minute
Vital lung capacity: predicted normal	5,100 c.c.	
actual	5,300 c.c.	

Electrocardiogram: normal; no change following operation. The physiological studies and heart size data before and after operation are shown in figure 2.

Case 3. A. G., a white boy, aged 16, had received a bullet wound in the left popliteal space eight months previously. Two weeks after the accident he resumed his usual physical activities, consisting of work on a farm and playing baseball whenever he was not otherwise engaged. His only complaint was fatigue and aching of the left leg after strenuous exercise.

Physical examination: A robust well developed boy in a normal state of physical fitness. The local phenomena of an arteriovenous fistula were present in the left popliteal space indicating a fistulous connection between the left popliteal artery and

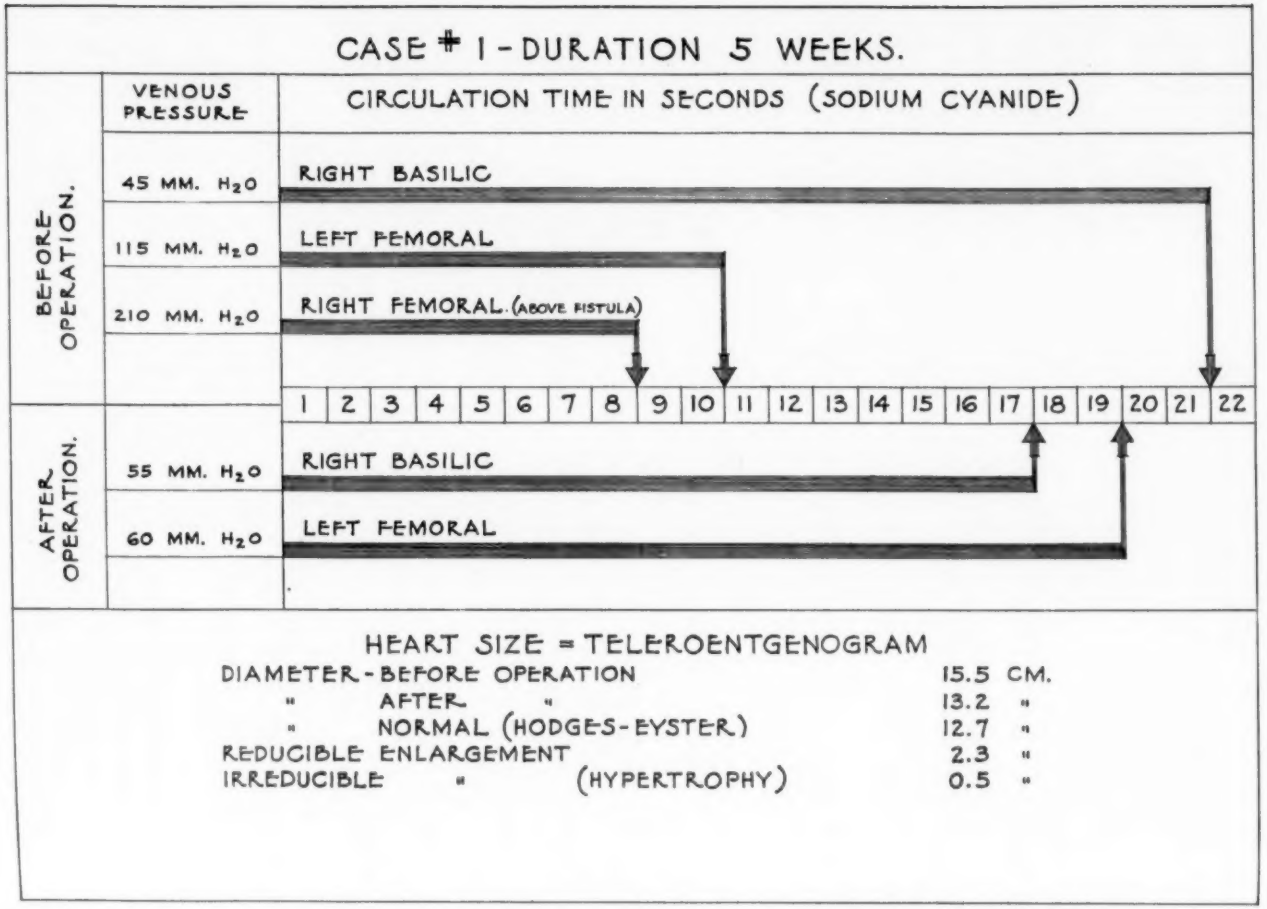
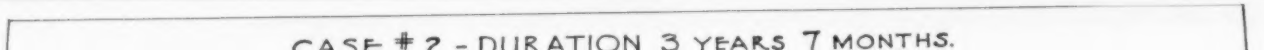

CASE # 1 - DURATION 5 WEEKS.
VENOUS PRESSURE
CIRCULATION TIME IN SECONDS (SODIUM CYANIDE)
BEFORE OPERATION.
45 MM. H2O
RIGHT BASILIC
115 MM. H2O
LEFT FEMORAL
210 MM. H2O
RIGHT FEMORAL. (ABOVE FISTULA)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
AFTER OPERATION.
55 MM. H2O
RIGHT BASILIC
60 MM. H2O
LEFT FEMORAL
HEART SIZE = TELEROENTGENOGRAM
DIAMETER - BEFORE OPERATION 15.5 CM.
" AFTER " 13.2 "
" NORMAL (HODGES-EYSTER.) 12.7 "
REDUCIBLE ENLARGEMENT 2.3 "
IRREDUCIBLE " (HYPERTROPHY) 0.5 "

FIG. 1. Case 1. Circulation time in seconds and venous pressure in mm. of H_2O and heart size before and after operation.



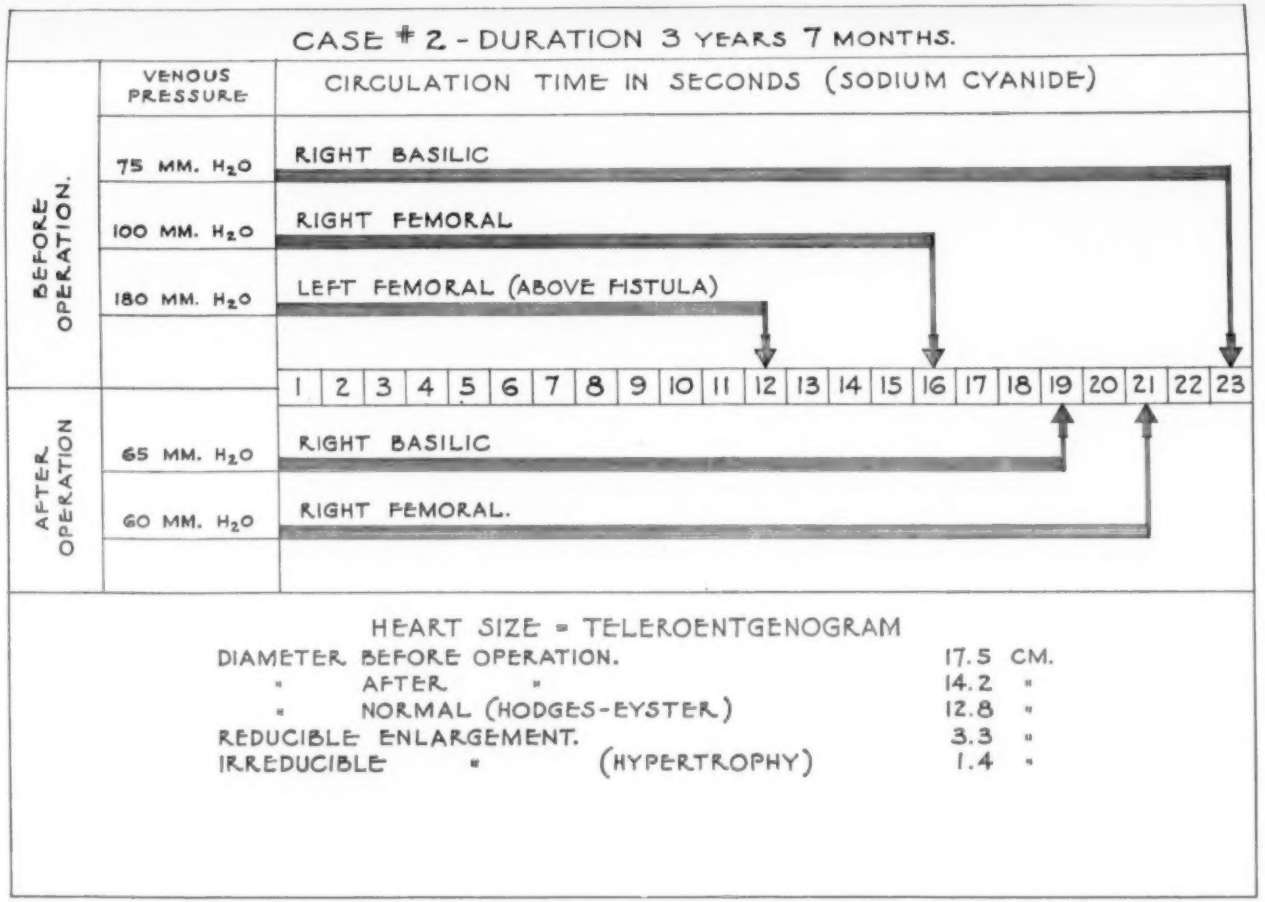

CASE # 2 - DURATION 3 YEARS 7 MONTHS.
VENOUS PRESSURE
CIRCULATION TIME IN SECONDS (SODIUM CYANIDE)
BEFORE OPERATION.
75 MM. H2O
RIGHT BASILIC
100 MM. H2O
RIGHT FEMORAL
180 MM. H2O
LEFT FEMORAL (ABOVE FISTULA)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
AFTER OPERATION
65 MM. H2O
RIGHT BASILIC
60 MM. H2O
RIGHT FEMORAL.
HEART SIZE = TELEROENTGENOGRAM
DIAMETER BEFORE OPERATION. 17.5 CM.
" AFTER " 14.2 "
" NORMAL (HODGES-EYSTER) 12.8 "
REDUCIBLE ENLARGEMENT. 3.3 "
IRREDUCIBLE " (HYPERTROPHY) 1.4 "

FIG. 2. Case 2. Circulation time in seconds and venous pressure in mm. of H_2O and heart size before and after operation.

vein. The neighboring superficial veins were definitely dilated. There was no edema of the left leg or ankle.

	Fistula opened	Fistula closed
Blood pressure	systolic 122, diastolic 60	systolic 126, diastolic 75
Pulse rate	90 per minute	76 per minute

Electrocardiogram: normal; no change following operation. The physiological studies and heart size data before and after operation are shown in figure 3.

Case 4. C. B., a negro farmer, aged 58, had received a bullet wound in the right thigh 21 years previously. Following the accident he remained in bed for 10 days. When the dressing was removed he noticed upon touching the upper part of the thigh a peculiar purring sensation which he states has continued and become more distinct. Since the healing of the wound he has worked regularly as a farmer with no discomfort except for the occurrence of cramps in the calf muscles of the right leg. There had been swelling of the right foot and leg for four years. He came for relief of the functional impairment and swelling of the right leg.

Physical examination: A well developed and nourished negro man lying comfortably in bed without subjective complaints. The local phenomena of an arteriovenous fistula were present 3 cm. below the apex of Scarpa's triangle on the right side indicating a fistulous connection between the right femoral artery and vein. There was a moderate degree of brawny edema up to the upper third of the right leg. The vessels above the fistula were greatly enlarged as far as they were palpable. The jugular bulb on the right side was markedly dilated but there were no pulsations above the auricular level. There were no phenomena indicating heart failure of the congestive type.

	Fistula opened	Fistula closed
Blood pressure	systolic 130, diastolic 65	systolic 146, diastolic 94
Pulse rate	84 per minute	56 per minute

Electrocardiogram: normal; no change following operation. Venous pressure and heart size data before and after operation are shown in figure 4.

Discussion

It is evident from these studies that cardiac dilatation is the principal factor concerned in the increase in cardiac size in arteriovenous fistula. The amount of actual hypertrophy is determined mainly by the duration of the fistulous connection (figure 5).

Lewis and Drury [1, b] concluded that the enlargement of the heart was primarily and chiefly a dilatation due to a deficient nutrition of the heart muscle, consequent on a fall of the mean arterial blood pressure occurring in arteriovenous fistulae. They did not believe there was increased circulating blood volume for in experiments on dogs an anastomosis of an artery and vein did not increase cardiac output unless there was a rise in general venous pressure, and no rise in general venous pressure occurs in arteriovenous fistulae without heart failure. Recently Laplace [5] and Quattlebaum [6] have expressed opinions in agreement with that concept of the pathogenesis of cardiac enlargement.

It is an established physiologic principle that the minute volume of cardiac output is dependent primarily upon the volume of the return flow to

CASE #3 - POPLITEAL ARTERY - DURATION 8 MONTHS.

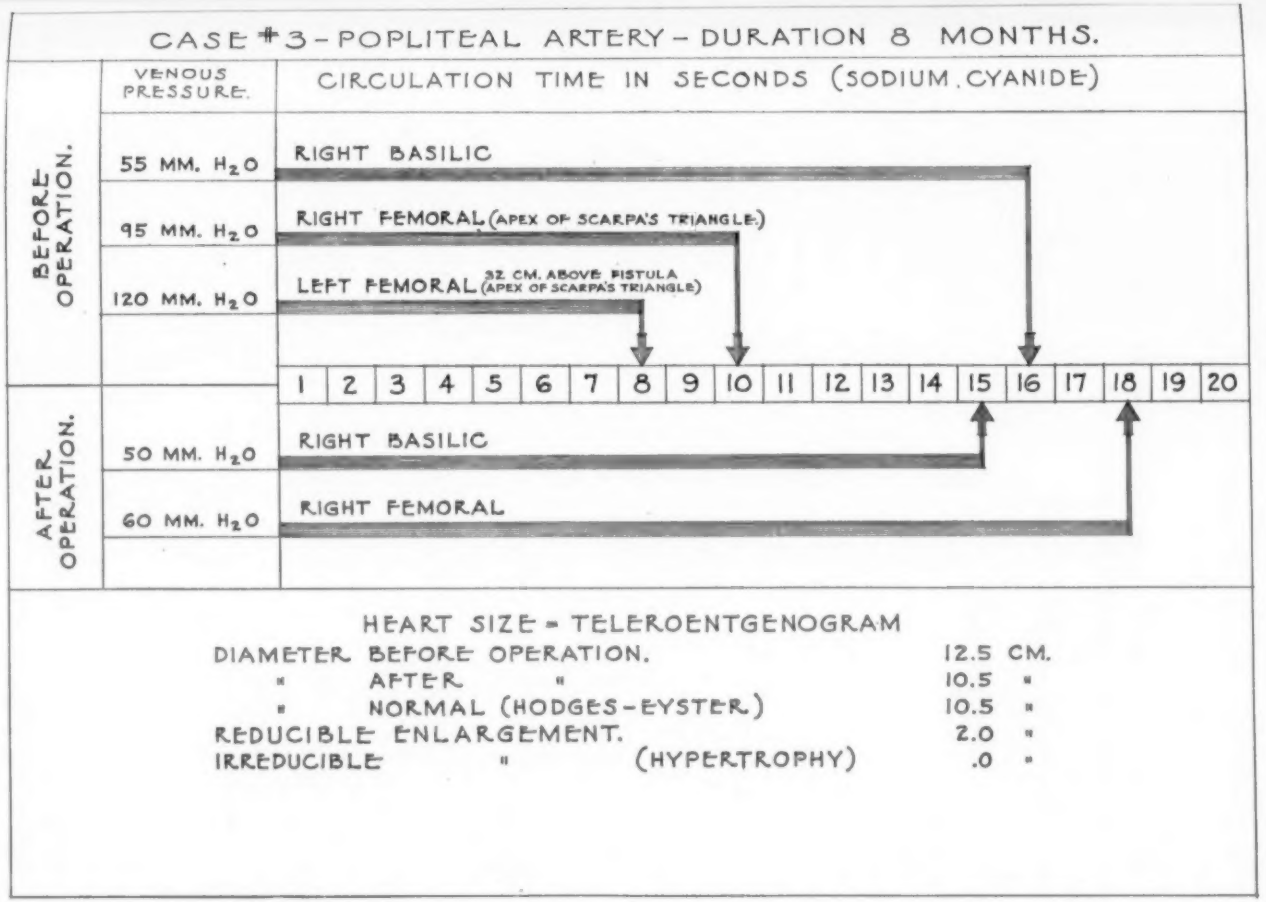

CASE #3 - POPLITEAL ARTERY - DURATION 8 MONTHS.
VENOUS PRESSURE.
CIRCULATION TIME IN SECONDS (SODIUM CYANIDE)
BEFORE OPERATION.
55 MM. H2O
RIGHT BASILIC
95 MM. H2O
RIGHT FEMORAL (APEX OF SCARPA'S TRIANGLE)
120 MM. H2O
LEFT FEMORAL (APEX OF SCARPA'S TRIANGLE)
32 CM. ABOVE FISTULA
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
AFTER OPERATION.
50 MM. H2O
RIGHT BASILIC
60 MM. H2O
RIGHT FEMORAL
HEART SIZE - TELEROENTGENOGRAM
DIAMETER BEFORE OPERATION. 12.5 CM.
" AFTER " 10.5 "
" NORMAL (HODGES-EYSTER.) 10.5 "
REDUCIBLE ENLARGEMENT. 2.0 "
IRREDUCIBLE " (HYPERTROPHY) .0 "

FIG. 3. Case 3. Circulation time in seconds and venous pressure in mm. of H_2O and heart size before and after operation. The femoral vein was used at a point corresponding approximately to a similar location as that in Cases 1 and 2.

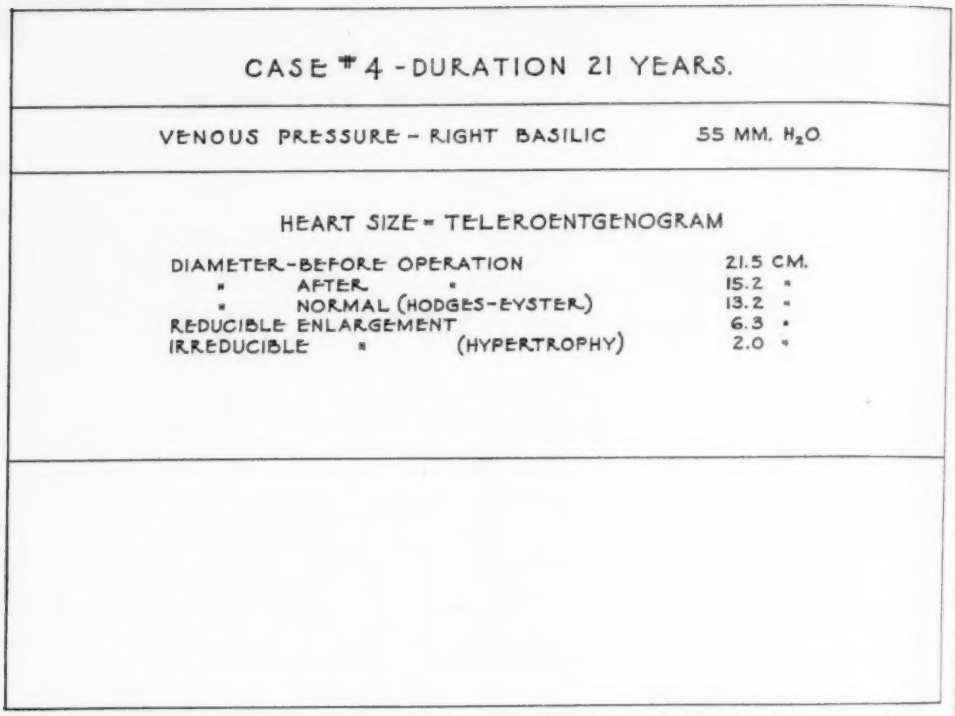

CASE # 4 - DURATION 21 YEARS.
VENOUS PRESSURE - RIGHT BASILIC 55 MM. H_2O
HEART SIZE - TELEROENTGENOGRAM
DIAMETER-BEFORE OPERATION 21.5 CM.
" AFTER " 15.2 "
" NORMAL (HODGES-EYSTER) 13.2 "
REDUCIBLE ENLARGEMENT 6.3 "
IRREDUCIBLE " (HYPERTROPHY) 2.0 "

FIG. 4. Case 4. Basilic venous pressure and the heart size before and after operation.

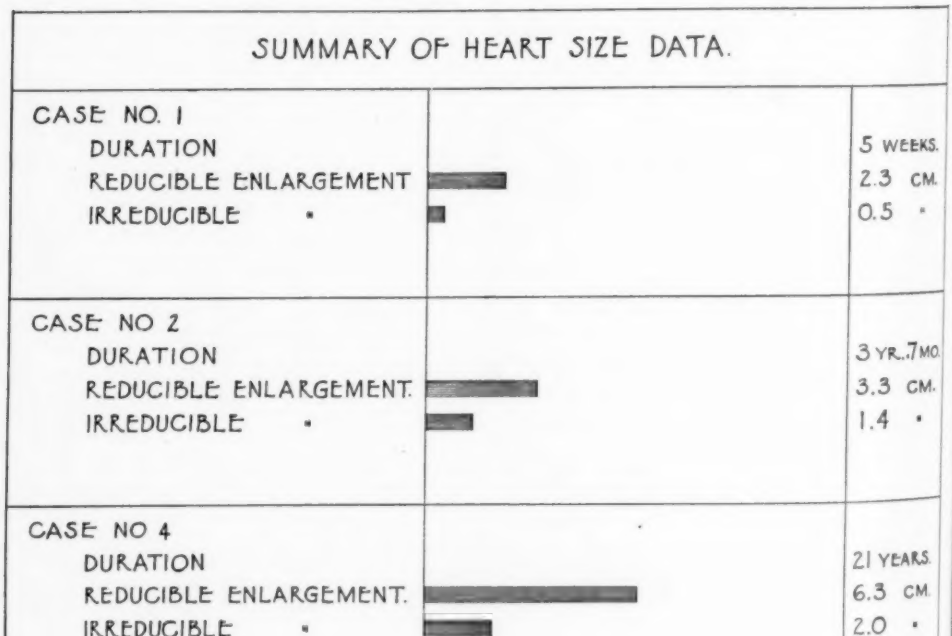


FIG. 5. Reducible and irreducible cardiac enlargement related to the duration of the arteriovenous fistula.

the right auricle, and the force of cardiac contraction is so perfectly adjusted to the quantity of blood which flows into the auricle from the veins that no stasis occurs with a rise of general venous pressure unless heart failure ensues.

The observations made on these patients show that all the factors which can increase the volume of return flow to the right heart operate in arteriovenous fistulae, and in these patients without heart failure there was no rise of general venous pressure.

That the dilatation of the heart is not due to a nutritional deficit of the myocardium is evident from the cases here studied. It is inconceivable that a nutritional factor could be responsible for so marked a degree of reducible dilatation continuing for a long period * and without the development of heart failure in men engaged in active physical labor. Furthermore, Green [7] has shown that in arteriovenous fistulae the decrease of coronary blood flow induced by a lowering of diastolic blood pressure is to a considerable extent mitigated by an increase in coronary blood flow during systole resulting from a relative lowering of the systolic peripheral coronary resistance in relation to aortic pressure. Through peripheral vascular constriction a normal mean blood pressure may be approximated and this, operating in conjunction with the augmented systolic coronary circulation, may result in an increase of coronary flow to or even above a normal minute volume.

The observations made on these patients indicate that the cardiac enlargement occurring in arteriovenous fistulae results from the following changes in the dynamics of the circulation.

1. (*a*) There is great increase in cardiac filling due to acceleration of the velocity of blood flow and increase of effective venous pressure in the involved vein and anatomically associated tributaries proximal to the fistulous connection.

(*b*) With adjustment dilatation of the artery and vein the rate of blood flow and the pressure in the vein decrease while the cross section of the column of the returning current increases.

(*c*) The enlargement of the artery and vein in the fistulous circuit and the increase in cardiac size are primarily an adjustment dilatation. Cardiac hypertrophy is responsible for only a small part of the increase in cardiac size.

2. An extreme degree of reducible cardiac dilatation, 21 cm. to 15.2 cm., can exist over a prolonged period (21 years) with the occurrence of only a minimum amount of cardiac hypertrophy and without the development of heart failure. This is not in agreement with the concept of a myocardial nutritional defect as the factor responsible for the changes in cardiac size.

* In this connection the observations made on Case 1 are of interest. The femoral artery was temporarily occluded by ligature. Within 24 hours the cardiac dilatation had reduced from 15.5 cm. to 13.4 cm. Due to the ischemic symptoms developing in the foot, the ligature was removed. Within 24 hours thereafter the heart again measured 15.5 cm.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

CONGENITAL ADHESIONS OF THE GALL-BLADDER *

By LESTER R. WHITAKER, M.D., F.A.C.S., *Boston, Massachusetts*

ABNORMAL peritoneal attachments to the gall-bladder are more common than inflammatory adhesions. Though often described these congenital adhesions [1] are not generally recognized, so strong is the obsession in the medical profession that all disturbances of the gall-bladder are inflammatory in origin. Yet, it should be obvious to the careful observer that these sheets of tissue, running from lesser omentum to gall-bladder, duodenum and colon, are simple folds of peritoneum having definite relations, definite structure, and regular arrangement of vessels. They cannot possibly be the result of inflammation. Often with these attachments there is no evidence of a past infection of the gall-bladder; in fact, many times the vesicle appears normal.

Inflammation as a result of infection has been over emphasized in pathological conditions of the gall-bladder—considered primary to everything—especially to gall-stones. Anatomical, mechanical and metabolic factors have been neglected. Even cholesterosis confined to the mucosa of the gall-bladder has been attributed to infection, though this is no more likely to be true than with atherosclerosis. It is probable that they are both degenerative diseases, from toxic or metabolic disturbance, with inflammatory effects.

There are two ways of determining whether or not the peritoneal attachments under discussion are congenital or inflammatory adhesions. The first, and most important, is their anatomical relations. The second is lack of evidence of inflammation in the gall-bladder itself.

Embryologically, the development of abnormal peritoneal attachments of the gall-bladder appears fairly simple. The primitive digestive tube has an anterior and a posterior mesentery. In rotation of the stomach the posterior mesentery becomes the greater omentum, and the anterior, the lesser omentum. In the anterior mesentery a bud grows out from the enteric tube to form the liver, bile ducts and gall-bladder. Ordinarily the anterior mesentery stops at the common bile duct and portal vessels, but it may be more extensive and run from the common duct laterally over to the gall-bladder, down to the duodenum, and to the hepatic flexure of the colon—even to the right lobe of the liver and to the lateral and posterior abdominal walls, perhaps closing the foramen of Winslow. There may be

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From the Department of Anatomy, Boston University School of Medicine and the Surgical Clinic of Massachusetts Memorial Hospitals, Boston, Mass.

much or little of this anterior mesentery, from a slight band of tissue running from the lesser omentum across to the cystic duct and down the front of the gall-bladder, to the extensive sheet of tissue described above. Or this sheet may become a loose veil with a mesentery to the gall-bladder, which means simply that the gall-bladder is enfolded and supported in the tissue. The sheet may be closely adherent to the gall-bladder over its surface or there may be two separate sheets, one running to the medial and one to the lateral margin of the vesicle, usually attaching to the liver on either side. The sheet may pass over the gall-bladder without attachment. The tissue may be absent above and below, leaving only a band from the lesser omentum across the duodenum to the anterior surface of the gall-bladder. It may be supplemented by another distinct band to the hepatic flexure of the colon. In all these types the general relations are the same except that different parts of the sheet of tissue may be missing.

Meyers and Bloom [2] in 1933, made a study of these congenital peritoneal adhesions in the upper right quadrant of the abdomen, but while stating that these definite structures described were not of inflammatory origin, they have contributed to the general misunderstanding with regard to their nature by the terms, "periduodenitis" and "pericholecystitis" or "essential periduodenitis." Because of confusion of terms and the frequency of this abnormality, surgeons may be led to make false operative diagnoses in many cases.

A resumé of literature by Meyers and Bloom shows that different authors have found, on the average, 20 per cent of abnormal peritoneal attachments about the gall-bladder and duodenum in apparently normal individuals. In 54 cadaver and autopsy specimens they themselves found membranes in 54 per cent. Only 5 per cent showed inflammatory adhesions.

In 51 cadavers examined by the writer at the Boston University School of Medicine definite abnormal peritoneal attachments to the gall-bladder were present in 45 per cent. All of the gall-bladders with these congenital adhesions appeared thin-walled and normal. All except one were in male cadavers. (There were not more than five or six females among the 51 subjects.) This is another fact which weighs against inflammatory origin, since cholecystitis is more common in the female.

Among 100 patients upon whom cholecystectomy was performed by me at the Massachusetts Memorial Hospitals 18 showed definite abnormal peritoneal attachments to the gall-bladder. Fifteen of these 18 patients were women. From a statistical point of view it is doubtful that sex is significant in this condition.

Following is a summary of the anatomical arrangement of congenital peritoneal adhesions in 23 cadavers and in 18 patients:

Twenty-three of 51 cadavers examined had definite congenital adhesions to the gall-bladder and duodenum. In this series the arrangement typical for such attachments prevailed, that is, a sheet of tissue running from the lesser omentum to the gall-bladder, along its border toward the fundus,

with bands running across the duodenum and to the hepatic flexure of the colon. In one case there was a small band about 2 cm. in width from the ampulla of the gall-bladder across the duodenum. All the others had attachments of at least two-thirds the length of the gall-bladder; three of them from the gall-bladder to the duodenum alone, and the other 20 from the gall-bladder to the duodenum and hepatic flexure of the colon. In two of these there were extra strands of peritoneal tissue running from the first and second parts of the duodenum up to the liver, but *in no case was any constriction of the duodenum produced.* In four of the 23 cases the foramen of Winslow was closed. One case with the extensive type of attachment described had, in addition, a short mesentery of the gall-bladder. Jackson's membranes were present in three, which does not show a large relationship with congenital peritoneal adhesions elsewhere. In two cases outside this series the author observed an extensive peritoneal attachment of the hepatic colon to the right lobe of the liver laterally, with none to the gall-bladder. In one other case an attachment ran from the liver to a point at a considerable distance along the transverse colon.

All the gall-bladders of this series in cadavers were thin-walled and apparently not inflammatory. There was one female among 22 males. The instances of inflammatory adhesions in the whole number of 51 were not recorded, but I am sure that there were not over 10—a much lower percentage than that of congenital adhesions.

In 18 patients from a series of a hundred cholecystectomies by the author at the Massachusetts Memorial Hospitals *a greater variety of abnormal attachments prevailed.*

In five cases there was a peritoneal sheet running the whole length of the gall-bladder; in four this was connected with the duodenum, and in two with the hepatic colon. *In one of these there was moderate constriction of the second portion of the duodenum.* The foramen of Winslow was closed in two.

In four cases there were small attachments running from one-third to one-half way down the gall-bladder. In all of these a band passed over the first or second part of the duodenum; and in one the foramen of Winslow was closed.

In two cases there was a loose veil of tissue running over the whole gall-bladder and attached to duodenum, colon and liver. In these two cases definite mesenteries of the gall-bladder were present. *In one of them there was a short strand running from the duodenal cap to the liver, producing some tension.* In both, the foramen of Winslow was closed.

In five cases there were sheets of tissue running across the gall-bladder at varying distances below the fundus, and attaching to the liver and posterior abdominal wall laterally. Four of these *showed bands running across the duodenum, two of which produced moderate constriction.* In three cases there were attachments to the hepatic flexure of the colon; and in three of the five the foramen of Winslow was closed. The appearance of one

case was described as a " sort of blanket thrown over the gall-bladder with the head and chest sticking out." In another case there was a second sheet running to the postero-lateral margin of the gall-bladder. The description here was, " the fundus of the gall-bladder looked almost like the head of a doll protruding from between the upper and lower blankets."

In one of these cases an unusual situation prevailed. I quote from the operative note, " Running from the lesser omentum and the first part of the duodenum across the fundus of the gall-bladder to the liver and then on to the second portion of the duodenum and hepatic flexure of the colon was a thin sheet of peritoneum-like tissue. This sheet of tissue ran downward, partially closing the foramen of Winslow. The arrangement was almost as though the gall-bladder were inside a case of tissue. The gall-bladder was not adherent to it and when this tissue was removed the peritoneal covering of the gall-bladder was intact." That there was no inflammation of the peritoneum was obvious when the gall-bladder was removed by dissecting its serosa.

In two cases the usual attachment was present, running from the lesser omentum along the gall-bladder from cystic duct to fundus. But then it was reflected posteriorly to the liver and abdominal wall, running across the duodenum and attaching to the hepatic flexure of the colon. There seemed to be in these two cases two distinct layers of tissue, anterior and posterior, 4 to 5 mm. apart, along the attachment to the gall-bladder.

Diagnostic Investigation

The question as to whether congenital peritoneal attachments to the gall-bladder, duodenum and colon produce definite symptoms is difficult to settle. It is important that efforts be made in this direction to throw more light on obscure symptomatology in the right upper quadrant of the abdomen; and to avoid unnecessary surgical interference, yet to be able to advise operation when indicated. No definite symptom picture presents itself. It may be that this very indefiniteness of the symptoms, such as vague discomfort in the right upper quadrant, anorexia or nausea, bloating, " sour stomach," or occasional sharp twinges of pain unrelated to meals, or perhaps increased following meals, are indications of anatomical disadvantages which prevent normal function.

Homans [3] who has made a careful study of symptomatology in 11 cases of " congenital transduodenal bands " has grouped symptoms under the headings of " intermittency," " food relief," " vomiting " and " bleeding." In his 11 cases, five had intermissions, some discomfort being more or less steadily present. Six of the cases showed a definite food relief, but in others taking of food excited discomfort. Vomiting was present in six of the 11 cases. In none was there a history of hematemesis.

In Homans' cases gastric analysis was of no value, some showing high and some showing low acidity.

Roentgen-rays in three of nine cases of Homans which were studied showed duodenal defects; two, dilatations of the upper duodenum; one, hour-glass stomach. In one, hyperperistalsis was present, and in another, an atonic stomach.

Homans' cases were diagnosed as everything else than "transduodenal bands," the question of this diagnosis being brought up in only two of them. The most common confusions were duodenal ulcer and chronic cholecystitis. Three of Homans' cases were neurotic.

Meyers and Bloom believe that for diagnosis combined examination of the gall-bladder and the gastrointestinal tract is of no advantage, and hold that fluoroscopy is not practical on account of failure of visualization of the gall-bladder. They attribute significance to a "shifting deformity" of "Duval." "Duval deformity is differentiated from ulcer deformity in that the latter is constant in any one segment of the cap, whereas the former is shifting. Duval's deformity is differentiated from irritable cap in that with the former the cap is filled but the deformity occupies a varying segment of the cap and is still irregular after atropine." The impression of Meyers and Bloom is that no clinical entity can be built up from the symptoms in these cases and that periduodenal adhesions of this type are not significant clinically.

In the study of the symptomatology in my series, seven of the cases had to be ruled out on account of the presence of gall-stones, leaving 11 for study.

In two of the 11 cases the duodenum was deranged somewhat; in one of these the first part was pulled up by a short strand running to the liver; in the other there was a slight constriction at the second part. Both of these cases had more or less discomfort in the epigastrium and right upper quadrant after meals, with nausea and vomiting. Both were subject to migraine. One of the two was relieved considerably by cholecystectomy and section of the adhesions; but the other was practically unrelieved. They were followed three and five years.

In three of the cases where the gall-bladder was greatly constricted by abnormal sheets of peritoneum running across it, there was discomfort and irregular pain in the right upper quadrant associated with more or less nausea and vomiting, the pain being worse after meals. Following removal of the gall-bladder and congenital adhesions in these cases, symptomatic relief was obtained after an average period of one month. This has lasted for two years in two of the cases. The other patient could not be located for follow-up.

In the two cases where a loose veil covered the gall-bladder with a mesentery, relief for three and five years was obtained after removal of the vesicle.

With four cases in which the abnormal attachments were of lesser extent, and there were symptoms of gas, indigestion, feeling of fullness with epigastric discomfort after meals, removal of the gall-bladder and adhesions

gave relief in one for three years. One, who had been subject to migraine was unrelieved after three years; two who were neurotic were unrelieved after several months.

From the above records it will be seen that relief appeared to follow operation in those cases where the gall-bladder was restricted in its motion by the congenital adhesions or where the motion was abnormally free through a mesentery. The possibility with the hypermobile vesicle is that kinking of the cystic duct interfered with emptying. In one of the two cases with mesentery a transverse constriction of the gall-bladder was shown by the Graham test, although emptying was only slightly delayed; but in the other the gall-bladder was exceedingly large and emptied abnormally slowly.

Although Meyers and Bloom do not believe that *fluoroscopy* is of value it seems that this means to aid the diagnosis should not be lightly given up. The combined examination of the gall-bladder and stomach, duodenum and colon has been suggested several times [4] and some studies have been carried out.[5] If the " double-oral " method of cholecystography is used [6, 7] the gall-bladder in most cases can be visualized under the fluoroscope. If the shadow presents irregularities on the roentgenogram, such as apparent pulling of the fundus toward the mid-line, and if there is lack of mobility under the fluoroscope, adhesions are suspected. If under combined examination the gall-bladder, duodenum and hepatic flexure of the colon can not be separated, or are distorted, adhesions are probable. However, with a thick or tense abdominal wall manipulation of the viscera may be so difficult that nothing can be learned in this way. If the shadow of the gall-bladder hangs low or has an unusual alignment, and is hypermobile under the fluoroscope, it may have a mesentery as well as other peritoneal attachments. However, in the 12 cases with congenital adhesions in which stones were absent the diagnosis of " perivesicular " adhesions was made in only two cases. But this was worth attaining and is encouraging to further effort.

The Question of Treatment

Rational treatment of these congenital right upper quadrant adhesions would depend upon definite diagnosis. If there were only moderate symptoms and a few abnormalities, like " shifting irregularity of the duodenal cap " [2] or " hypo-mobility " or " hyper-mobility " [5] of the gall-bladder, medical treatment should certainly be tried first. It appears that a considerable number of these patients are neurotic. The relation here may be that neurotic individuals magnify slight symptoms produced by interference with motility of these organs in their normal physiological activities; or there may be functional disturbances elsewhere such as " irritable colon." These congenital adhesions might in many cases adjust themselves by stretching without an operation. Then, too, it must be remembered when contemplating operation that the postoperative adhesions might be more restrictive than

the congenital. On the other hand if the patient has severe symptoms such as inability to hold food on the stomach to a dangerous degree, together with signs of irregularity or torsion of the duodenum or gall-bladder, operation is advisable.

In the case where the previous diagnosis has not been made and congenital adhesions are found at operation, the question arises as to what to do. Constricting bands should certainly be relieved. It seems to me that the gall-bladder should be removed also. It is not a necessary organ and in all probability the dire results attributed to its loss have been exaggerated. If for good reason a surgeon exposed my gall-bladder I would thank him to remove it even though it appeared normal, provided of course, it were done with little trauma to abdominal viscera and without damage to the liver. During an operation for the removal of gall-bladder and congenital adhesions it must be kept in mind to leave as little raw surface as possible. In some cases it might be advisable to remove the gall-bladder and then only to relieve restricting bands, allowing a considerable amount of the peritoneal tissue to remain to prevent postoperative adhesions which might occur on surfaces from which it had been removed.

Summary and Conclusions

Congenital peritoneal adhesions to the gall-bladder are much more common than is ordinarily realized since they are found in about one-fourth of the population.

That many of these adhesions, or bands, do not produce symptoms is probable; but that some of them do is almost certain.

The symptom picture is hazy. It consists chiefly of vague right upper abdominal discomfort or pain—stabbing or dragging, intermittent or more or less constant—usually worse after meals, and often accompanied by nausea or vomiting. Neurotic symptoms may be prominent.

Preoperative diagnosis is difficult. It depends upon: The above symptom picture; the elimination of other causes of right upper quadrant pain; under combined roentgenoscopy, lessened or increased mobility of the gall-bladder in relation to other viscera—perhaps tenderness.

Treatment should be: First medical, with a view to reducing the alimentary load for a more or less crippled digestive system; second, psychological.

Surgery should be reserved for those cases where the roentgen-ray, including fluoroscopy, shows abnormalities; where other measures fail; and where pain and/or nausea and vomiting are severe.

Operative treatment consists in removal of the gall-bladder and section of constrictive bands or sheets of peritoneal tissue. Care must be taken to prevent secondary adhesions, or these may become more troublesome than the primary.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

SAMUEL JONES GEE AND HIS FRIENDS*

By Sir Humphry Rolleston, Bt., G.C.V.O., K.C.B.

Perhaps the best way I can join in a tribute to Joseph Hersey Pratt—the clinical physician—is to offer a sketch of another clinical physician, at St. Bartholomew's Hospital, with some sidelights on contemporary medical London when I was a student there half a century ago. The names of great physicians have often been linked by their admirers with recently recognized forms of disease, and also with favourite prescriptions—the least of their achievements. Samuel Jones Gee is an example of this eponymous association. Fifty years ago what is now known as posterior basal meningitis or, as Still showed in 1898, chronic meningococcal meningitis of infants was colloquially known in London as "Gee and Barlow's disease" after their account in 1878 of cervical opisthotonos in infants which in his aphorisms Gee later summarized as follows: "not a tuberculous affection; it is due to a chronic meningitis of the medulla. It may, however, occur as a symptom in tuberculous affections of this region." In 1899 Sir Thomas Barlow (1845–) and David Bridge Lees (1846–1915) gave an expanded account of the condition under the title of "posterior basic (occlusive) meningitis; acquired hydrocephalus." These three writers were colleagues at the Hospital for Sick Children, Great Ormond Street, W. C.

In 1888 Gee published an article of four pages "On the Coeliac Affection" beginning "There is a kind of chronic indigestion which is met with in persons of all ages yet is specially apt to affect children between one and five years old." At the time it attracted very little attention perhaps because, like most of his original papers, it appeared in the *St. Bartholomew's Hospital Reports* and not in the medical periodicals with their much wider circulation. In 1903 W. B. Cheadle (1836–1910), his colleague at the Hospital for Sick Children, gave an account of cases under the name of "acholia" and ascribed them to "inhibition of the liver"; Sir Byrom Bramwell (1847–1931) of Edinburgh in several papers between 1901 and 1915 described the condition as pancreatic infantilism; C. A. Herter (1865–1910) of New York "rediscovered" the disease in 1908 and started metabolic investigation of what he termed infantilism due to intestinal infection; Heubner (1843–1926) in the following year followed on the same lines, and the disease was sometimes called Gee-Herter and Herter-Heubner disease. The eponym "Gee's disease" appeared in 1926 in *The Manual of the International List of Causes of Death, as Adapted for Use in England and Wales, Scotland and Northern Ireland*, by the Registrar General; this tabular list contained a number of terms used by practitioners in signing death certifi-

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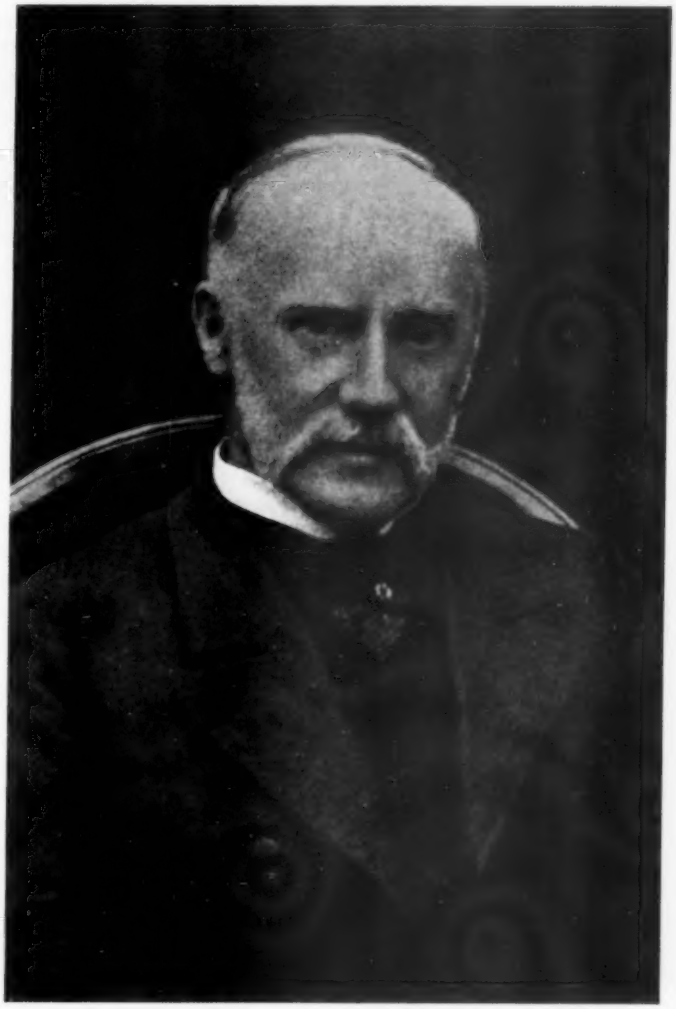
cates, and thus differs from *The Nomenclature of Diseases, Drawn up by a Joint Committee Appointed by the Royal College of Physicians of London* (1931) which gives very few synonyms and does not include "Gee's disease." The comprehensive article on this disease by Izod Bennett, Hunter, and Vaughan in 1932 was entitled "Idiopathic Steatorrhoea (Gee's Disease), A Nutritional Disturbance Associated with Tetany, Osteomalacia, and Anaemia." Since 1926 Thaysen of Copenhagen has written 10 papers arguing that the coeliac affection, non-tropical sprue, and tropical sprue should be grouped together under one designation "idiopathic steatorrhoea," and Mogensen of Copenhagen in 1937 suggested the eponym "Gee-Thaysen's disease" for those three conditions. Henry Moore and his Dublin colleagues recommended that the coeliac disease of children should be called the "Gee-Herter disease," that idiopathic steatorrhoea of adults and adolescents of non-tropical countries should be known as the "Gee-Thaysen disease, and that the name sprue for the tropical disease should be retained." Years before his paper on the coeliac affection Gee's name became familiar in connection with a linctus composed of equal parts of compound tincture of opium, syrup of tolu, and oxymel of squill. It was said that this prescription was not his, but that of a lady bountiful of a village, who had thus cured the obstinate cough of one of his hospital patients. It became widely popular, and in Smithfield, at the doors of the hospital which so freely supplied it to out-patients, "linctus tarts" were on sale. It is interesting to recall his philosophical indifference to posthumous fame as merely meaning "the number of times after death the letters composing the man's name were put together in one order" (Legg).

Samuel Jones Gee was born on September 14, 1839, in London where his father, William Gee, was in business but was much interested in literature and frequented the British Museum. His mother Lydia Sutton (1797–1888) was, like many mothers of great men, a remarkable woman. His parents were somewhat puritanical. Gee, the only one of their four offspring to survive infancy, was a delicate boy and never robust. When eight years old he went to a private school in Enfield, a few miles from London, and from 1852 to 1854 he attended University College School. Three years later he matriculated at the University of London, and as a medical student of University College Hospital came under the influence of Sir William Jenner (1815–98), whose example may in some degree have accounted for Gee's successful dogmatic teaching at the bedside. In 1861 at the final examination for the degree of bachelor of medicine at the University of London he was bracketed with C. Hilton Fagge (1838–83) for the gold medal and the University scholarship in medicine; in 1865 he proceeded to the M.D. degree and became a member, being elected five years later a fellow, of the Royal College of Physicians of London. In the meanwhile he had become a member of the Royal College of Surgeons in 1863, and been appointed resident house surgeon to Richard Quain (1800–87) at University College Hospital in December 1862; earlier in that year he had been resident

house surgeon at the Hospital for Sick Children, Great Ormond Street. This hospital, the first solely for children in London, was founded in 1852 on the site of the mansion of that medical Maecenas, Richard Mead (1673–1754), largely as the result of the exertions of Charles West (1816–98), an



Samuel Gee

almost exact contemporary of Sir William Jenner; from 1848 to 1860 West lectured at St. Bartholomew's Hospital Medical School on Midwifery, with which at that time diseases of children usually were nominally combined. It was not until 1904 that a special department for diseases of children was

established at St. Bartholomew's Hospital, and was then placed under the care of Sir A. E. Garrod (1857–1936) and Dr. H. Morley Fletcher, physicians to the Hospital and also on the staff of the Hospital for Sick Children and the East London (now Princess Elizabeth of York) Hospital for Children respectively. In Gee's time and for some years after, almost all the members of the staff of the Hospital for Sick Children were also attached to general Hospitals. Gee was appointed assistant physician in May 1865, physician in February 1875, and consulting physician in March 1885 to the Hospital for Sick Children. Like Thomas Addison and Hilton Fagge, particularly as regards dermatology, he was anxious to avoid the reputation of a specialist in any branch of medicine, and removed from the *Medical Directory* his title of consulting physician to the Hospital for Sick Children.

That Gee was house surgeon at University College Hospital and at the Hospital for Sick Children might now suggest that he inclined more to surgery than to internal medicine. But it is perhaps not generally realized that the post of house physician is more modern, at any rate in name, than that of house surgeon. At the Hospital for Sick Children the separate post of house physician was first established in December 1879. During the first half or more of the last century the work now done by house physicians was at most hospitals part of the duties of a resident medical officer, known as the apothecary, a title then in use for general practitioners. Thus at St. Bartholomew's Hospital, London, Frederick Wood (1820–1906) was apothecary from 1847 to 1867 and performed the work later carried out by 14 qualified medical men, namely 10 house physicians, two junior assistant physicians, and two casualty physicians. In December 1867 four house physicians were created, and within a quarter of a century increased to ten. At Guy's Hospital the Stockers, father and son, were apothecaries, and the first resident house physician was appointed in 1868, a non-resident junior house physician being added in the following year; a house surgeon had been appointed in 1856. At the Radcliffe Infirmary, Oxford, there was a resident house-surgeon-apothecary until 1860 when a house physician was appointed; the last house-surgeon-apothecary but one there holding office for 12 years. At University College Hospital the name house physician at any rate was in use many years earlier, as is shown by the following information courteously supplied by the Secretary:

> From its opening in 1834 the Hospital had an apothecary and a house surgeon. On December 7, 1841 the Medical Committee recommended that, as the duties of house-physician have always been performed by the apothecary, the titles as well as the duties of these offices be united, and after 1845 "house physician" often occurs in the Minutes. In 1851 on the recommendation of the Medical Committee the title apothecary was changed to resident medical officer, and in May 1880 that of "physician's assistant" to that of house physician.

In 1868 Gee was elected assistant physician to St. Bartholomew's Hospital. It was then quite exceptional for the larger teaching hospitals in London to go outside their own school in order to fill vacancies on the permanent staff of the hospital. Indeed 20 years later a score of young would-be physicians were waiting about in the hope of becoming one of the eight on

the medical side of the staff. During this period of probation the aspirants held minor teaching posts, such as demonstrators, in the medical school, or in connection with the hospital, such as medical registrars, on a salary so nominal as to be quite insufficient to keep body and soul together. The competition was extremely severe and exacting, for it was not customary for the future consultants to engage in ordinary general or family practice; scholarships and grants for scientific research were then rarely available, and men without private means had to take pupils or undertake literary or other work to scrape together a living and to keep up appearances. It was then and for years after a common complaint that many able men could not afford to become consultants. The waiting time might be exceptionally tedious, especially when as very occasionally happened, several resignations and deaths occurred unexpectedly within a short time, and as a result the successors in office being comparatively young enjoyed an unusually long tenure of office, while their juniors had therefore to face a correspondingly increased period of probation. At St. Bartholomew's Hospital in the 'sixties of the last century the mortality among physicians was very high:

William Baly (1814–61) in whose memory there is a gold medal for distinction in physiology at the Royal College of Physicians of London, was killed in a railway accident near Wimbledon; W. S. Kirkes (1823–64), distinguished for his work on embolism, the now forgotten hypothesis that chorea is due to miliary embolism in the corpora striata, and author of a textbook on physiology subsequently edited for many years by W. D. Halliburton (1861–1931), died from double pneumonia and pericarditis, a combination much more frequent then than now; Sir George Burrows (1801–81), afterwards president (1871–76) of the Royal College of Physicians of London, resigned in 1864; Henry Jeaffreson (1810–66) succumbed to typhus fever caught from a fatal case in a medical student under his care; G. N. Edwards (1830–68) died of renal disease; Robert Martin (1827–91) resigned in 1868 on account of a nervous breakdown when engaged to be married; this was a tragedy, for he soon recovered completely and returned to professional practice the next year in London; but a career of the brightest promise was irreparably wrecked, for "in London to step aside for a time is to be left behind." He was a charming white-haired gentleman with old-fashioned courtly manners, who often came to the post-mortem room or, as his generation called it, the dead house, and was an expert in the facial diagnosis of the cause of death. He died of pneumonia, of which he had previously had an exceptional number of attacks; in 1869 F. J. Farre (1804–86) automatically ceased to be an active physician to the hospital on attaining the age-limit of 65 years.

The way was thus opened for those waiting at St. Bartholomew's Hospital, such as James Andrew (1829–97), Reginald Southey (1835–99), Sir William Church (1837–1928), and also for fresh blood; besides Gee, there were elected Sir Dyce Duckworth (1840–1928) in 1869 and Sir Lauder Brunton (1844–1916) in 1875, both Edinburgh graduates. Wickham Legg (1843–1921), like Gee, a pupil of Sir W. Jenner to whom, soon after Gee's election to St. Bartholomew's Hospital, Sir James Paget said "Can't you send us another Gee?", was appointed to succeed Gee there as demonstrator of morbid anatomy in 1874, and as lecturer in that subject and assistant physician in 1878. He had qualified in 1867 and about this time was tutor to Prince Leopold (1853–84), the fourth and youngest son of Queen Victoria; this appointment was probably due to Sir William Jenner who from 1861 was the influential medical adviser of Her Majesty. Prince Leopold was the subject of haemophilia on which Legg subsequently (1872) wrote

a treatise. In 1883 he was selected by the president (Jenner) to deliver at the Royal College of Physicians of London the Bradshaw lecture founded in 1875 in memory of Dr. W. W. Bradshaw of Oxford. He chose " Cardiac Aneurysm " as his subject, and it may be noted that in 1889 Norman Moore (1847–1922) gave this lecture on " The Distribution and Duration of New Growths," and that Gee in 1892 followed in these footsteps of his juniors by lecturing on " The Signs of Acute Peritoneal Diseases." Legg's most considerable medical book was on " The Bile, Jaundice and Bilious Diseases " (1880). In 1887 he retired from St. Bartholomew's Hospital and medicine to devote himself to liturgical subjects and bringing out numerous volumes for the Henry Bradshaw Society for editing rare liturgical texts, being Chairman of its Council from 1895 to 1915. Henry Bradshaw (1827–89), University Librarian, (1867–89) at Cambridge, and much interested in mediaeval liturgies inspired Moore, when a turbulent undergraduate at St. Catherine's, with an interest in palaeography. Gee, Legg, and Norman Moore who contributed 454 lives, mainly of medical men and Irish Saints to the first 63 volumes of the *Dictionary of National Biography* and others to its two supplements, formed a small group of colleagues, resembling the scholar-physicians in the time of Linacre (1460–1524), the founder and first president of the Royal College of Physicians of London. Other like-minded contemporaries were W. A. Greenhill (1814–94), J. F. Payne (1840–910), and James Finlayson (1840–1906) of Glasgow; of these Norman Moore, the youngest and not the most profound, was probably the most successful in popularizing the history of medicine.

At St. Bartholomew's Hospital Gee was, for a short time in 1870, in charge of the skin department, established in 1867. This was in accordance with the rule then in force there that the assistant physicians and assistant surgeons should take charge of the special departments, and was in reality a compromising expression of the widespread dislike then felt by the leaders of the profession against specialism, a survival of the dictum that " a specialist is half a quack," ascribed to Sir Benjamin Brodie (1783–1862) who was president of the Royal Society, the Royal College of Surgeons of England, and the General Medical Council. Gee found a more congenial occupation as demonstrator of morbid anatomy (1870–74), and lecturer on pathology from 1874 to 1878 when he became physician to the hospital and joint lecturer on medicine. In obedience to the age limit of 65 years he became consulting physician in 1904.

In 1901 he was appointed honorary physician to the Prince of Wales, afterwards King George V. It has been suggested that his inability to yield to the weaknesses and foibles of mankind may have influenced the distribution of public honours as far as he was concerned; but probably, like Gallio, he " cared for none of these things." Indeed according to tradition, when asked by a most influential personage if he would like to be made a baronet, he replied that he would prefer a fur coat.

With his clear and logical mind and after a most careful clinical examination of the patient Gee arrived at his diagnoses, which were very seldom wide of the mark, by an orderly process of exclusion and not by intuition. Osler spoke of him as combining the spirit of Hippocrates with the method of Sydenham. He was one of the best clinical teachers of his time in London, and his hospital rounds, made in the early afternoon, as is the custom in London, on three days in the week were always crowded; he naturally concentrated attention on the new cases, his opinion on nervous diseases being much quoted. Competition to be one of his clinical clerks for three months was keen, and to be his house physician, then resident for a year, W. H. R. Rivers (1864–1922) being the last under this arrangement, was a prize indeed. His house physicians, probably unconsciously, often adopted some of his peculiarities, such as turning back the lowest inch of their coat sleeves before examining a patient; this was a protection against parasitic invasion, and long before the time of white linen coats. The *Medical Notes* (1921) dedicated "to the Memory of My Teacher Samuel Gee" by Sir Thomas (now Lord) Horder, inevitably recall the collection of "Clinical Aphorisms from Dr. Gee's Wards (1895–96)" which he published in 1897. In the early 'eighties of the last century clinical medicine received comparatively little help from laboratory methods, clinical pathology being introduced at St. Bartholomew's Hospital in the next decade, mainly by A. A. Kanthack (1863–98) the first whole-time teacher of pathology in the London medical schools. But I saw Gee sit down in one of his wards to stain sputum for tubercle bacilli soon after Koch described the method in 1882. As his colleague and friend Sir Thomas Barlow wrote, he was one of "the group of great Victorian physicians who held firmly the inseparable link between morbid anatomy and clinical medicine."

At the Royal College of Physicians of London Gee was much in request; he held various offices and gave the following lectures: In 1871 the Goulstonian lectures on "The Heat of the Body"; this lectureship founded in 1632 by Theodore Goulston, M.D., F.R.C.P. is given to "one of the four youngest doctors of the College," and it was further directed that a dead body should if possible be provided, a suggestion long ignored; the Lumleian lectures in 1899 on "The Causes and Forms of Bronchitis and the Nature of Pulmonary Emphysema and Asthma"; these lectures were endowed in 1581 by Richard Caldwell (1513–84), president of the College in 1570, and John, Baron Lumley (? 1534–1609), and was originally called in the annals of the College the Chirurgical Lectures; and the Bradshaw lecture which, as mentioned above, is of comparatively modern origin.

The Harveian Oration—the most honorable and perhaps the most difficult to discharge—Gee declined, perhaps more than once. It was founded in 1656 by William Harvey with a number of directions, some of which long ago fell into abeyance; for example, it was last delivered in Latin more than 70 years ago, and the complete commemoration by name of all the benefactors of the College is never attempted now. The reason suggested for

Gee's refusal was that being doubtful about the value of experiment in the natural sciences he felt that he could not obey Harvey's direction to exhort the fellows and members " to search and study out the secrets of nature by way of experiment." At the present day this attitude seems very strange; but Gee lived much in the past and preferred the old to modern ways. It should, however, be mentioned that when Augustus Matthiessen (1831–70), lecturer on chemistry at St. Bartholomew's Hospital Medical School, and C. R. A. Wright discovered apomorphine in 1869 they handed it over for physiological investigation to Gee, who not only tried it on animals but was the first human being to be submitted to its action with the result that his initial scepticism about it being " a most powerful emetic and contrastimulant " was, as he fully admitted later, decisively demolished.

Gee's personality was complex and therefore impressed people in different lights; he was thought by some to be shy and reserved, by others to be fastidious; he certainly was not a good " mixer " or of the " hail fellow well met " fraternity. An unfavourable first impression was experienced by two of his life-long colleagues and friends.

Francis Harris (1829–85) was elected assistant physician to the Hospital for Sick Children, Great Ormond Street, in 1859 and, in 1861 to St. Bartholomew's Hospital, becoming full physician in 1868; he was thus Gee's senior colleague; the two men were very different, Harris being a Cambridge graduate of independent means who rather avoided private practice and was much devoted to field sports. He had heard much about Gee, but without being attracted to him. On one occasion when in poor health, he was advised by his friend Thomas Smith (1833–1909) to go away and get someone to take his out-patients; " Yes," said Harris, " but if there is one person I will not put on duty it is that beast Gee." He, however, was persuaded to do so, and eventually he and Gee became the greatest friends. In his appreciative memoir Gee described a curious incident in connection with Harris's only published work—his thesis for the M.D. degree on " The Nature of the Substance Found in Amyloid Degeneration of the Various Organs of the Human Body " (1860). Not being accustomed to write for the press, Harris made little use of stops and in letters substituted dashes; in his thesis he followed his usual style, but when faced with the proofs was horrified by the numerous dashes which the printers had conscientiously copied.

Howard Marsh (1839–1915), surgeon to St. Bartholomew's Hospital and the Hospital for Sick Children, professor of surgery (1903–15) and Master (1907–15) of Downing College, Cambridge, described after Gee's death, the very frigid reception he received at their first meeting when he arrived, confessedly a day late, to succeed Gee as house surgeon at the Hospital for Sick Children, where later he and Sir Thomas Smith were Gee's colleagues and were instrumental in securing his election to the assistant-physiciancy at St. Bartholomew's Hospital. Marsh also mentioned Gee's outspoken criticism of men, how with his " eyes glowing with indignation and intense conviction " he would declare " the man is a scoundrel."

From Wickham Legg's *Recollections of Samuel Gee,* published in 1915, the following may be quoted, the first two *obiter dicta* having a somewhat Johnsonian flavour; " Sir, I have forgotten more anatomy than you ever knew "; " Yes, Mill was an able fellow, but Bain was a dunderheaded Scotchman "; his dismissal of the *Handbook of Therapeutics* (1869) by his contemporary Sydney Ringer (1835–1910) as " a book of little dodges "; of the sudden death of Andrew Marvell the younger (1621–78) he said that it was not due to poison, but that he " was only murdered by his doctor who refused to give him the bark for a tertian ague." Many stories about him were current at St. Bartholomew's Hospital, some apocryphal and even inherited from John Radcliffe (1658–1714). He was opposed to speculation, often quoting *hypotheses non fingo,* was profoundly critical and sceptical, and frequently changed his expressed opinion.

He was prone to be pessimistic; thus in 1886 in a letter to Legg he sounded a despondent note: " the struggle for life is so hard that those in the medical profession who are able to care for anything but making money are quickly becoming very few. The learned physician is almost extinct. And I am sorry for it, because the rank which the profession takes in the world depends chiefly upon the physicians." During the intervening 50 years the distribution of the relative spheres of influence has been much modified. Of the modern Universities founded in the nineteenth century in England, including his own, that of London, he had a poor opinion. When he had reached the three score years and ten of the psalmist he looked back without any satisfaction; care of his own health became something of a tyrant, and he concluded that life was but a sorry thing. Describing himself as an " Old Whig " he had a contempt for politicians, did not read their speeches, and thought badly of this country's future.

Wickham Legg who saw much of him heard him laugh heartily once only; Gee, however, had humour though generally dry and often so subtle that it escaped detection by the ordinary individual. But there are exceptions to most rules, and Norman Moore, when laid up in Norfolk with an attack regarded as malarial, received from him the following lines:

> " I want to know, Moore, if you mean
> To write a treatise on the spleen,
> And if we find it does not plague you
> To follow up with one on ague."

He hardly ever went to the theatre; painting, architecture, and music did not appeal to him in the least. Norman Moore shared this lack of feeling for music, and could recognize one tune only, that of " God save the King," because every one then stood up. Gee loved the birds and flowers of the country. Like his teacher, Sir William Jenner, he strongly opposed the admission of women to the medical profession. He was essentially a lonely soul, especially after the death of his wife and one of his two daughters. Even as a younger man he preferred his own fireside to the

meetings of medical societies, at which his voice was little heard. But at the premier medical society in London, the Royal Medical and Chirurgical (expanded in 1907 into the Royal Society of Medicine), he sat on many committees and was honorary librarian (1887–99), being succeeded by Norman Moore. He certainly was not one of "the three Gs," three slightly junior contemporaries, so-called in the late seventies of the last century from their constant activities at medical societies in London; they were Sir W. R. Gowers, (1845–1915), Sir James Goodhart (1845–1916) and W. S. Greenfield (1846–1919), afterwards professor of pathology (1881–1912) at Edinburgh.

Extremely learned, Gee had read very widely from Hippocrates onwards and, though always pleased to discover that what was put forward as a new observation, had been anticipated by the Greeks he kept abreast of the modern German and French works on medicine. His favourite medical writers were Hippocrates, Sydenham and Heberden. His carefully trained memory seemed to retain all he read. His range of general literature was also extensive, especially of philosophy; he was attracted by the stoics, particularly Marcus Aurelius and Epictetus, and by the Cambridge Platonists; in 1872 he translated into English verse the hymn of Cleanthes (B. C. 300). Poetry, especially Wordsworth, appealed to him, and he was said to have known the whole of the "Prelude" and much of Pope's poems by heart; other favourite authors were Milton, George Herbert, Pascal, Montaigne, and Walter Scott. Matthew Arnold he spoke of as "the poet of despair." He was more in sympathy with the writers of the seventeenth and eighteenth centuries than with those of subsequent years. After his death it was said that he might have been a professor of English literature and equally well have occupied a chair of philosophy. With such encyclopaedic knowledge it is hardly surprising that he had a supreme contempt for any pretence of learning and hated a display of extensive reading. From the paucity of references in his published papers it would seem probable that he considered long lists of references as evidence of the author's vanity.

As a writer Gee began early and his concise style, which gave the maximum information in the fewest words possible, characterized his writing from the start, "thrift in words" being one of his mottoes. Sir John Russell Reynolds (1828–96), physician to University College Hospital enlisted with great success among the eminent contributors to his well-known *System of Medicine* in five volumes (1866–79) two young men from those under his eye at the hospital; Gee before he was thirty wrote in the first two volumes on chicken-pox, scarlet fever, and tuberculous meningitis, the last especially being an admirable study of the natural history of the disease. The other was Sir William R. Gowers who supplied classical articles on diseases of the blood-forming organs, being probably thus led to invent his haemocytometer (1877) and haemoglobinometer (1878), before his name became so predominantly associated with neurology—the branch of medicine which then especially attracted able young physicians.

Gee took much trouble in the choice of words, and preferred an English to any foreign word; thus " all of one mind " was better than " unanimous " and " hereafter " than " for the future." Legg thought that he took special interest in a man with dysentery who, when asked what he complained of, answered " Sir, the bloody flux." It was not unnatural that when asked in the closing years of the last century to write the article on pleurisy in Allbutt's *System of Medicine*, the successor of Russell Reynolds' *System*, he stipulated that no editorial changes should be made in what he had written. Later in conversation he expressed his dislike of " what is called getting up the literature " and this no doubt weighed with him in selecting T. J. (now Lord) Horder to revise the article for the second edition in 1909. But this expression of opinion was a few years before his death, and he had practised as well as preached the precept never to write on a subject until the literature had been thoroughly mastered. He contributed 46 papers to the *St. Bartholomew's Hospital Reports*, but wrote two books only. The first *Auscultation, Percussion Together with Other Methods of Physical Examination of the Chest* appeared in 1870 and reached a fifth edition in 1907, the fourth edition being dedicated to the memory of Laennec. The text was largely composed as he walked to the hospital, when he would turn into a side street to jot down a sentence just constructed. From its logical form it has been compared to Euclid's propositions, and in 1901 he remarked " this book taught me more in the writing than it will teach anyone else in the reading." The other book *Medical Lectures and Aphorisms* appeared in 1902 and was dedicated to the memory of Sydenham. It passed into a fourth edition in 1915 when Wickham Legg added to it his " Recollections of Samuel Gee " with a signed and pleasing photograph. It contained 272 aphorisms of which 258 had been collected by J. T. Horder in 1897 who was his house physician and follower; they condensed a vast amount of practical medicine. The following may be quoted:

No. 59. " Pneumonia is not a local, but a universal disease; and the brunt of it may fall upon any part—lungs, endocardium membranes of the brain, intestines, kidneys."

No. 81. " Pericarditis is not so common now as formerly; a fact which must be attributed to the use of sodium salicylate in the treatment of rheumatic fever. Endocarditis, however, seems to be as common as ever."

No. 231. " Tache cérébrale is a sign of little or no value."

No. 257. " There is often a remarkable latency about diseases of old people. Phthisis particularly is often overlooked because of its supposed improbability."

No. 258. " As a rule people do not die ' of old age.' There is usually failure of a particular organ, and not of all together. Still, it is sometimes very difficult to say exactly from what an old person does die."

Gee's important paper on "The Clinical Enlargement of the Spleen in Hereditary Syphilis and Some Other Diseases in Children" was read on March 26, 1867 before the Royal Medical and Chirurgical Society. He showed that in the early stages of congenital syphilis the spleen was palpably enlarged in half the cases and reached a considerable size in a quarter of the cases; the mortality in the second category was very high, and the degree of splenomegaly was therefore an index of the severity of the infection. The paper, however, was not considered to be worthy of publication in the Society's *Transactions;* this was not a unique mistake in the somewhat erratic decisions of the Society's referees; for the same judgment was passed on the paper on the open-air treatment of tuberculosis in 1862 read by Henry MacCormac (1800–86), and on several papers between 1857 and 1860 on the recently described Addison's disease, though not by Addison who much resented this ruling. As Gee's paper was never published in full there was some misconception about its contents, and accordingly Sir Thomas Barlow at the great debate on visceral syphilis at the old Pathological Society of London in 1875 loyally asserted the value of Gee's conclusions. At one time Gee drew up a plan for a history of medicine, and he published a paper on "Sects in Medicine" (1889) and on Abraham Cowley (1903); but unfortunately he soon gave up the larger project.

Gee married on December 7, 1875 Sarah, daughter of Emanuel Cooper, a member of the Society of Friends, whom in the formal, old-world manner of speech, which in his young days had suggested that he too was a Quaker, he described to one of his colleagues as being "quite adequate." His best man was Robert Bridges (1844–1930) who was his pupil at St. Bartholomew's, a colleague as assistant physician at the Hospital for Sick Children and poet Laureate in 1913. In his *Carmen elegiacum de Nosocomio Sti. Bartolomaei Londinensi* (1877), dedicated to Patrick Black (1813–79), whose house physician he had been, Bridges summarized, in Ovidian verse, the characteristics of the staff, containing references to Gee such as: Tute, Gei, mihi quam dulce et habuisse magistrum.

Gee died suddenly in an anginal attack on August 3, 1911, when with his surviving daughter at Keswick on the English Lakes; a necropsy, for which he had left instructions with his lawyer, showed extensive atheromatous change in the aorta and aortic valves. He left an estate of £34,879, not a large sum for a successful consulting physician.

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CASE REPORTS

ANEMIA AS THE CAUSE OF SEVERE CONGESTIVE HEART FAILURE: REPORT OF A CASE*

By ELMER C. BARTELS, M.D., F.A.C.P., *Boston, Massachusetts*

THAT anemia can be the primary cause of organic heart disease is doubtful; it can, however, give rise to quite abnormal subjective and clinical signs. For such disturbances to arise it is necessary for the anemia to be severe. It may be of the type characterized by a low level of the hemoglobin and a moderate reduction of the erythrocytes or of the type in which both factors are reduced. Certain criteria are necessary before a diagnosis of heart disease attributable to anemia can be made; namely (1) presence of a marked anemia, and (2) disturbance of cardiac function.

Herrick and Nuzum,[1] in 1918, first called attention to the association of pernicious anemia with angina pectoris. They found four cases among 200 cases of angina pectoris. Coombs,[2] in 1926, in a series of 36 cases of pernicious anemia found this combination in nine. Cabot,[3] in his book published in 1926, mentioned three cases of intense and typical angina and pernicious anemia without changes in the coronary arteries. Herrick,[4] in 1927, described three more instances, in two of which necropsy disclosed arteriosclerotic change of the coronary arteries. He remarked on the rarity of the association.

Willius and Giffin,[5] in 1927, reported an incidence of 43 cases of angina in 1,560 cases of pernicious anemia. These were cases in which the anemia was of long standing. The angina had the same clinical features as the angina of coronary disease, but there were no changes detected in the heart and the electrocardiograms were normal.

Reichel,[6] in 1929, reported a series of 114 instances of pernicious anemia with angina pectoris present in three. Gwyn,[7] in 1932, in a consideration of angina pectoris and anemia stated his opinion that the coronary artery must have undergone some pathologic change to produce the syndrome. The absence of angina pectoris in most cases of severe anemia was suggested as being attributable to the fact that the entire heart has degenerated and hence the ventricular balance is not upset. Case reports on this subject by many authors [7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18] have appeared.

Gunewardene,[19] of the Indian Medical Service reported in 1933 on the frequency of heart failure in ankylostomasis. In these cases severe anemia and marked cardiac dilatation accompanied by signs of congestive failure were often present. On treatment and cure of the infection the heart returned to normal size and the murmurs disappeared. Smith,[20] in 1933, made an electrocardiographic study of the heart in 15 cases of severe anemia. The blood pressure in seven of these was normal. In none were characteristic alterations of any sort found, in any phase of the electrocardiographic deflections.

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From the Medical Department of Lahey Clinic, Boston, Massachusetts.

Pickering and Wayne,[21] in 1933, reported on 25 cases of anemia. Eight of these patients complained of substernal pain with or without exertion. In six cases pain did not continue after the anemia had been cured. In two it persisted. The occurrence was not restricted to any particular type of anemia. The tolerance to exercise seemed to improve with the elevation of hemoglobin, but pain could still be produced with greater exertion. In four severely anemic patients the same exercise no longer produced pain or tightness in the thorax when the level of hemoglobin in the blood was 50 per cent.

Elliott,[22] in 1934, reported a case of anemia, caused by repeated severe uncontrollable epistaxis, with severe angina in the presence of healthy coronary arteries and aorta. The heart at necropsy weighed about 601 gm. There was no clinical evidence of hypertension. The cardiac hypertrophy was explained on the basis of the chronic anemia. The stress of exertion together with the acute loss of blood was felt to be sufficient to precipitate myocardial ischemia with resultant angina pectoris. The electrocardiogram showed alterations in the R T segment.

Ball [23] reported a case in which changes in the heart were demonstrated by roentgenology in the presence of severe anemia. This was a case of severe menorrhagia from fibroids in which there were definite symptoms of myocardial failure with enlargement of the heart and murmurs. After surgical removal of the uterus the murmurs disappeared and the roentgenogram revealed reduction in the size of the heart on return of the blood to normal.

In severe anemia certain changes in function of the cardiovascular system do occur. In the early stage the pulse rate increases and then an elevation of the blood pressure appears with a relative decrease in the pulse pressure. This changes later into a true cardiac and vascular insufficiency. A recent report by Grünberg [24] based on 111 cases, 49 of which were cases of pernicious anemia and 62 of secondary anemia, demonstrated this change. Changes in the size of the heart were also noted with enlargement to the right and left as the anemia progressed.

Changes in the cardiovascular mechanism during anemia are entirely the result of an attempt at compensation. Fahr and Ronzone [25] studied the circulatory compensation for deficient oxygen capacity of the blood in severe anemia and found that there was an increase in the minute volume output of the blood in addition to a lowered viscosity of blood and that the skin capillaries were contracted to half normal size in an effort to increase the blood flow through the vital organs. One can conceive of this attempted compensation going to the point where partial or complete failure of the heart ensues.

Case Report

A white man, a printer aged 76 years, was admitted to the hospital June 12, 1935, complaining of severe dyspnea on exertion and orthopnea of three months' duration. A family history of diabetes and of numerous gastrointestinal diseases was obtained. He had been married for 30 years and had had no children. His past history was essentially negative except for a history of indigestion for 15 years associated with vomiting of blood on two occasions and black stools on one occasion. All three of these episodes were 15, 13 and 11 years before admission respectively. For years he had taken soda to relieve his epigastric pain which usually came on one hour after eating. He had never had distress at night. For the last year he had taken soda

almost every day because of epigastric pain. He had been watching his stools carefully but had not noticed gross blood or tarry stools.

Three months before admission the patient had begun to notice dyspnea on walking up a slight incline to his office. He had no associated pain in the thorax. The dyspnea seemed to get worse each day and although he did not stop walking, when he arrived at his office he was gasping for breath and it was necessary for him to sit down and rest. He consulted his physician five weeks before admission and was told he was jaundiced and had a severe anemia. A potent preparation of liver was prescribed which the patient continued to take for five weeks. No improvement resulted. His dyspnea progressed so that it appeared on the slightest exertion. It was impossible for him to lie down and sleep, so he sat in a chair most of the time. Prior to onset of his illness he had lost about 10 pounds in weight, but in the last three months his weight had increased gradually and swelling of the entire body had occurred.

Examination on admission to the hospital revealed an extremely pale old man with moderate swelling of the face. His weight was 206 pounds. The blood pressure taken while he was at rest in bed was 154 mm. of mercury systolic and 74 diastolic. The pulse rate was 100 beats per minute and was regular. There was a slight icteric tinge to the sclerae and a suggestion of jaundice of the skin. His voice was quite hoarse and there was an irritating, non-productive cough. The pupils which were small and irregular reacted sluggishly to light. The teeth were all absent. The thyroid gland could not be palpated. The thorax and arms were edematous so that pressure produced deep pitting. No gross pleural fluid could be detected but coarse râles were heard through the lower portion of both lungs. The heart was percussed slightly to the left of the midsternal line. Its tones were distant, regular and no murmurs were present. The abdomen contained a large quantity of free fluid. The abdominal wall showed marked pitting edema. Although the liver was not palpable there was definite tenderness in the right upper quadrant of the abdomen. The scrotum and penis were moderately edematous and the legs revealed marked pitting edema. The rectal examination was essentially negative.

The laboratory studies revealed the number of erythrocytes to be 1,800,000 per cubic millimeter of blood. The value for hemoglobin was 35 per cent. The total leukocyte and the differential counts gave normal results. The urine had a specific gravity of 1.020, was alkaline in reaction and contained a trace of albumin. The phenolsulphonphthalein test was 45 per cent in two hours. The value for non-protein nitrogen was 28 mg. and for urea nitrogen, 17.7 mg. The value for serum protein was 6.4 gm., for cholesterol, 96 mg., for blood sugar, 120 mg.; for serum bilirubin 2.6 mg. and for blood chloride, 531 mg. per 100 c.c. The Hinton reaction of the blood was negative. The venous pressure was 22 cm. The stools were found to contain blood. Analysis of gastric content revealed a total acid of 54 and a free acid of 36.

Because of the marked edema and since the kidney function was apparently normal, measures to induce diuresis were instituted. The patient was given ammonium chloride, the intake of fluid was restricted and 14 c.c. of salyrgan were administered in divided doses in 15 days. Marked diuresis resulted, the patient losing 60 pounds. His general condition improved as the edema lessened and when his weight reached 146 pounds, he said that he felt fine and the edema and orthopnea had disappeared.

Investigation was instituted immediately to determine the source of the blood in the stools which had persisted in spite of a meat-free diet. The patient's condition was so improved that roentgenologic studies of the stomach were carried out and these revealed a persistent niche at the juncture of the first and second portions of the duodenum with a rather marked narrowing at this point.

A diagnosis of duodenal ulcer with chronic bleeding and severe secondary anemia was made and dietary treatment and administration of large doses of iron were begun. At the time the patient was dismissed from the hospital, or 25 days after admission,

the erythrocyte count was 3,080,000 and the value for hemoglobin 44 per cent. One and a half months later the erythrocyte count was 5,260,000 and the value for hemoglobin, 94 per cent. At that time also the patient's weight was 151 pounds. He felt perfectly well and was back at work. He did not have the slightest evidence of dyspnea on walking, slept flat in bed and had no evidence of gastric distress. At present, one and a half years after his dismissal from the hospital, he is in good health and is working every day.

Comment

On admission to the hospital this patient presented all the features of severe cardiac decompensation. His condition responded to administration of diuretics in the usual way for primary heart disease with failure. On alleviation of the secondary anemia the patient was able to return to his activities and his cardiac symptoms disappeared. This patient had the usual amount of arteriosclerosis for patients of his age, but there was no associated hypertensive or valvular disease and no history to suggest myocardial infarction. That the anemia was the precipitating factor in the decompensation of the heart seems certain and is further borne out by the course of the disease. No digitalis has been used by the patient since he was dismissed from the hospital.

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THE DIAGNOSIS OF SOLITARY LIVER ABSCESS BY MEANS OF THOROTRAST HEPATOSPLENOGRAPHY

Report of a Case *

By Wallace M. Yater, M.D., F.A.C.P., and John R. Cavanagh, M.D.,
Washington, D. C.

During the past five and one-half years we have employed Thorotrast for the purpose of demonstrating lesions of the liver and spleen in several hundred patients. This method of roentgenographic diagnosis was developed mainly by Oka [1] and Radt [2] about 1929. It consists in the intravenous injection of 50 to 75 c.c. (for adults) of a stabilized colloidal solution of thorium dioxide manufactured under the name of Thorotrast,† following which roentgenograms of the abdomen are made. The thorium dioxide is rapidly engulfed by the reticuloendothelial cells of the body, and because it is radiopaque it is possible to demonstrate the size, shape and structure of the liver and spleen, which contain these cells in greatest concentration. Cirrhosis of the liver and neoplasms are particularly well shown. Although thorium dioxide is somewhat radio-active and remains for years in the body we have not observed serious immediate or remote ill effects from its use. Yater, Otell and Hussey [3] have reviewed their first 200 patients examined over a period of five years and have failed to note harmful results. They describe the technic and the information that can be derived from the study of hepatosplenograms. Their first patient has recently returned for a checkup five and one-half years after the injection of 60 c.c. of Thorotrast. Although the roentgenogram shows shadows of the liver and spleen almost as dense as originally, she is in the best of health, in spite of the fact that the diagnosis of chronic lymphatic leukemia was made by competent clinicians six years ago and roentgen-ray treatment employed therefor.

* Received for publication February 15, 1937.
From the Georgetown University School of Medicine.
† Manufactured by the Heyden Chemical Company.

The opportunity to demonstrate liver abscess by means of hepatosplenography does not present itself often and we feel justified in reporting a case. Reeves and Apple [4] used Thorotrast for this purpose successfully in a case of amebiasis reported in 1933.

Case Report

Clinical Course. A white barber, aged 38 years, entered Georgetown University Hospital on July 24, 1936. Prior to May 10, 1936 he had been well since childhood, when he had had measles, mumps, pertussis and chicken-pox. On May 10, 1936 he had developed a severe attack of pain in the right upper quadrant of the abdomen which radiated to the right axilla. After a few days he had returned to work in spite of continued but less severe pain. Six weeks before admission the pain became worse and fever was first noted. The pain was practically continuous from then on and the fever persisted. The pain was described as sharp and stabbing, starting about 8 cm. to the right of the umbilicus and radiating to the right costal margin. There was also a dull, constant ache in the right lumbar region. For three weeks before admission he had vomited at intervals. A loss of 40 pounds had resulted. On the day before admission a chill had occurred. There had been no bowel disturbance.

The patient appeared to be seriously ill. There was no jaundice. The temperature was 101° F., the pulse rate 100, and the respiratory rate 22 per minute. There were numerous carious teeth, the tongue was dry, and the tonsils were hypertrophied and slightly inflamed. The heart and lungs appeared normal, and the diaphragm moved normally bilaterally. The abdomen was flat and symmetrical. On deep palpation there was marked tenderness over the lower portion of the right lobe of the liver, which could be felt about 6 cm. below the right costal margin and seemed to have a rounded edge. The hemoglobin was 56 per cent; the red blood cells numbered 3,180,000 and the white blood cells 26,050 per cu. mm. of blood, with 82 per cent polymorphonuclear neutrophiles. Other laboratory studies including urinalysis, van den Bergh reaction, bromsulphthalein test of liver function, Wassermann and Kahn tests of the blood, and repeated stool examinations were normal or negative.

During the first two and a half weeks in the hospital the temperature was very irregular and ranged from 98° F. to 103° F., being elevated practically every day. The condition became progressively worse, and a bronchitis aggravated the pain. Abscess of the liver was suspected early and it was decided to make hepatosplenograms. On July 27, 28 and 29, by intravenous administration 25 c.c. of Thorotrast were given, and on July 30 a roentgen-ray film was made of the abdomen. The appearance of the film, interpreted in conjunction with the clinical course, was definitely that of a large solitary abscess of the right lobe of the liver. Further roentgen-ray films were made at intervals after operation.

On August 10, 1936, Dr. William C. Gwynn opened the abdomen and found the right lobe of the liver to be enlarged with a rounded edge, and a rounded mass about the size of a medium-sized orange projected from its under surface. The omentum and parietal peritoneum were sutured to the anterior surface and edge of the liver adjacent to the mass, and a gauze packing was placed in the pocket thus formed. Two days later the incision was re-opened and an aspirating trocar and cannula inserted through the isolated area of liver into the mass. About 150 c.c. of thick reddish brown pus were aspirated, after which a large rubber drainage tube was placed in the abscess cavity and the area again packed with gauze. Pus continued to drain in gradually diminishing amount. Amebae or other organisms were not found in the pus, but a course of injections of emetine hydrochloride was given. On the tenth day after operation the tube was removed and the wound slowly healed. The irregular fever continued for three weeks after operation, when the temperature be-

came normal. The patient was discharged as cured on the fortieth day after operation.

On March 10, 1937 the patient was re-admitted to the hospital. He had remained well until one week before, when he became feverish and weak. During this week he had had several chills, and tenderness had developed in the upper right quadrant of the abdomen. Examination revealed slight enlargement of the liver, tenderness near McBurney's point, and dry râles in both lungs. The temperature on admission was 104.6° F.; the pulse rate was 120 and the respiratory rate 20 per minute.

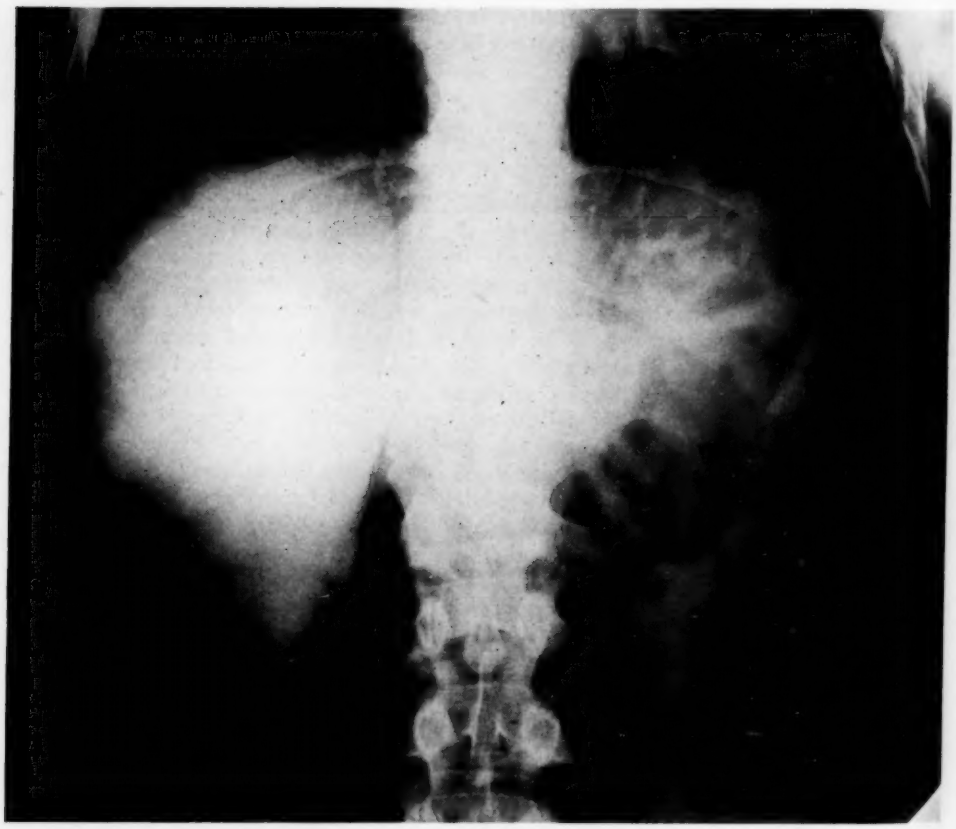

FIG. 1. Pre-operative hepatosplenogram, showing enlarged right lobe of liver with large area of lessened density in lower portion, the demarcation not being clear cut.

The blood pressure was 85 systolic and 58 diastolic. The urinalysis was normal. The hemoglobin was 57 per cent; erythrocytes numbered 3,600,000 and leukocytes 14,800 per cubic mm. of blood, with 84 per cent polymorphonuclear neutrophiles. A roentgenogram of the chest showed an area of opacity in the middle of the right lung field, which was thought to indicate interlobar pleurisy. A barium study of the colon showed a constant area of narrowing of the transverse colon, which was thought to be due to an adhesion from the old operative scar. A hepatosplenogram was made; this did not throw any light on the present illness. Several stool examinations were negative for amebae. A blood culture was negative. The Craig test for amebiasis gave questionable results. The temperature became normal after

ten days. The hemoglobin and erythrocyte count gradually rose to normal, while the leukocyte count rose to 17,000. The course of injections of emetine hydrochloride was repeated but not until after the temperature had been normal for several days. The patient left the hospital after four weeks, apparently well. The exact cause of the liver abscess or of the second illness was not determined.

Description of Hepatosplenograms. The first films showed the right lobe of the liver to be moderately enlarged downward (figure 1). There was normal hepatic opacity in the upper three-fifths of the liver shadow, but the lower rounded portion

FIG. 2. Hepatosplenogram made two weeks after operation for solitary abscess, showing abscess cavity about half its original size.

was relatively non-opaque. The upper rounded edge of this non-opaque area was not sharp but was rather " fuzzy," characteristic of an abscess without a well formed wall. The left lobe of the liver was not enlarged, and the spleen was of normal size. Films made two days before operation were quite similar. A hepatosplenogram made two weeks after operation showed the abscess cavity to be about half its original size (figure 2.) One month after operation the right lobe of the liver was practically normal in size, and the abscess cavity was about one-fourth its original size. Two months after operation there was a small mottled area of somewhat less opacity than the main mass of liver in the lower edge of the right lobe (figure 3). Apparently the

abscess cavity had contracted and become filled in with reparative tissue. The reproductions of these hepatosplenograms show far less detail than the films themselves. The hepatosplenogram made in March 1937 showed no appreciable change from the previous one.

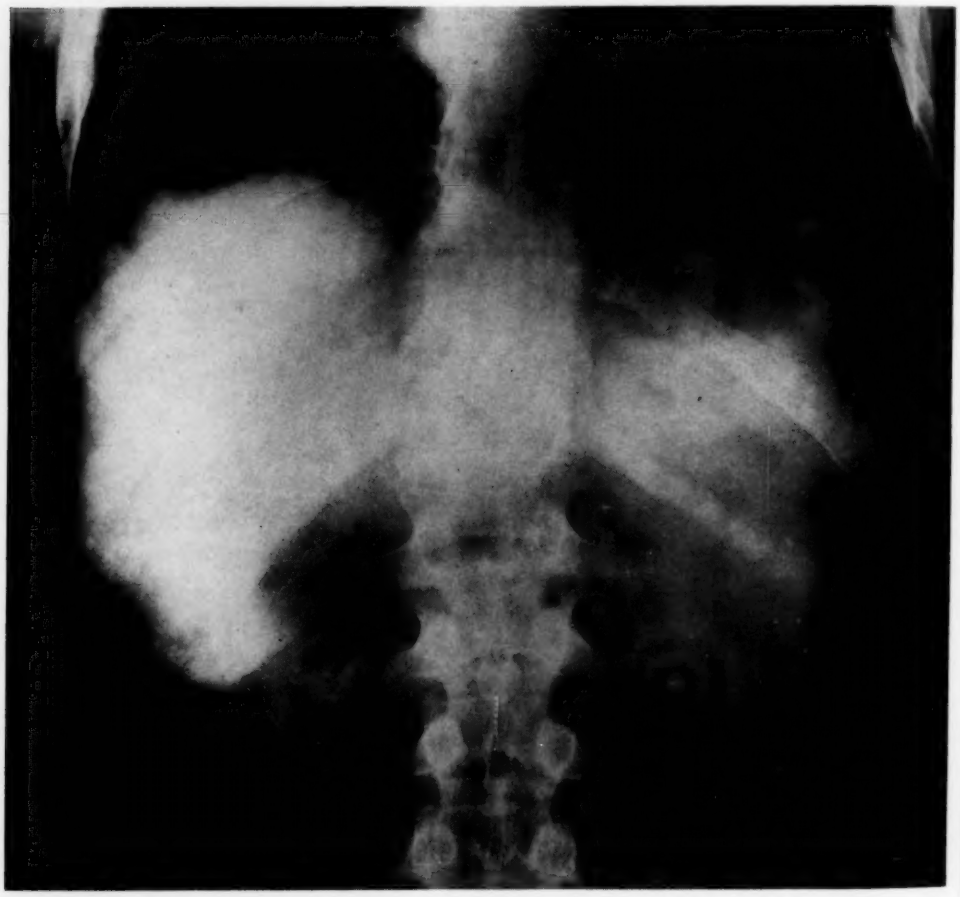

FIG. 3. Hepatosplenogram made two months after operation, showing healed area in lower portion of right lobe of liver.

COMMENT

The conditions that must be differentiated from solitary abscess of the liver in hepatosplenograms are neoplasm and cyst. Neoplasms, especially metastatic carcinoma, are usually multiple. They appear as round areas of lessened opacity with a clear cut edge and often a halo of condensed liver tissue about them. Solitary tumors of the liver are rare but have a sharper outline than abscess. The same is true of echinococcus cyst. While the outline of an abscess is irregularly circular, it is not sharp but " fuzzy " and blends with the adjacent liver parenchyma. It has a homogeneous appearance in its central portion as does a neoplasm, since pus does not contain reticulo-endothelial cells, at least

none capable of removing foreign bodies from the blood stream. The roentgen appearance should be pathognomonic when the clinical history is considered in conjunction with it. Hepatosplenography is merely a laboratory method of diagnosis and should be employed by the clinician and roentgenologist with the clinical picture in mind, although often a correct diagnosis of hepatic lesions can be made from a study of the films alone.

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EDITORIAL

BENIGN LYMPHOCYTIC CHORIO-MENINGITIS

In 1925 Wallgren [1] collected and described under the term "acute aseptic meningitis" a group of cases of meningitis which began abruptly and ran a benign course, which showed a lymphocytosis in the cerebrospinal fluid from which no bacteria could be isolated by smear or culture, and in which the recognized diseases capable of causing this symptom complex could be excluded. Since this publication many similar cases have been reported both in America and in Europe, and the condition is evidently not uncommon.

The clinical picture has varied considerably. The onset may be preceded by symptoms of an acute respiratory infection, or of "influenza." More often it is abrupt, with severe headache, fever, drowsiness, photophobia, vomiting and stiffness of the neck. In the mildest cases headache may be the principal complaint, and after an illness of two or three days, the symptoms may subside and permanent recovery ensue. More often the illness lasts from one to several weeks, but recovery eventually occurs without sequelae. In other cases the symptoms are more severe. There may be delirium, dizziness, marked drowsiness or excitability, restlessness and apprehension. Anorexia and constipation are usually marked. Transient pareses or even paralyses, usually of the cranial nerves, have been described, but there are no outspoken paralyses, as in poliomyelitis. There may be respiratory disturbances. Kernig's sign is often positive. Reflex disturbances are common; either exaggeration, diminution, or inequality of the deep reflexes. There is often slight swelling of the optic discs. Viets and Warren [2] have reported one case that died after convulsive seizures.

The cerebrospinal fluid has been found under increased pressure. The fluid is colorless, clear or slightly turbid. The cells are always increased, usually from 200 to 2000 or more above the norm, and over 90 per cent are lymphocytes. The lymphocytosis persists for several weeks in convalescence. In the severer cases the globulin is increased and the sugar and chlorides somewhat diminished. Cultures are sterile and tubercle bacilli are not found. The colloidal gold test may show a meningitis type of curve.

In the case of Viets and Warren there was a marked lymphocytic infiltration of the meninges, which extended deep into the brain substance along the vessels. There were areas of degeneration and gliosis, and in places the nerve cells showed inclusion bodies.

Recent investigations have shown that in a limited number of these cases the disease is due to a filtrable virus. This was first isolated by Armstrong

[1] WALLGREN, A.: Une nouvelle maladie infectieuse du système nerveux central? Acta Paediat., 1925, iv, 158.

[2] VIETS, H. R., and WARREN, S.: Acute lymphocytic meningitis, Jr. Am. Med. Assoc., 1937, cviii, 357.

and Lillie in 1933 [3] from the brain of a monkey, the sixth in an inoculation series, the first of which had been inoculated with the brain emulsion of a human case supposedly of encephalitis of the St. Louis type. In 1935 Scott and Rivers [4] isolated a virus, later found to be identical, from the cerebrospinal fluid of two human cases of the disease, by intracerebral inoculation into mice. Traub [5] also obtained the same virus from a colony of mice which had been naturally or accidentally infected.

Intracerebral inoculation into mice of infected cerebrospinal fluid or virus suspensions causes an encephalitis in most of the animals. The symptoms appear after five to six days and consist chiefly of tremors, clonic convulsions, and tonic spasm of the hind legs. The virus is present in the brain, but also in the blood and other organs. At necropsy the animals show a lymphocytic infiltration of the meninges and choroid plexus and a virus bronchopneumonia. Those which survive are immune to reinoculation.

Monkeys can be infected by intracerebral inoculation, and the disease may spread spontaneously among them.

Guinea pigs are highly susceptible, both to intracerebral and subcutaneous inoculation. After seven or eight days they show fever, which may be the only symptom, loss of weight and signs of general illness. The distribution of the virus and the lesions are like those in mice. Guinea pigs which survive become immune, and their serum will neutralize the virus and prevent the infection of other mice or guinea pigs. The serum of human cases has also acquired protective power, but this develops only after six to ten weeks.

Because of the characteristic pathological lesion the disease caused by the virus is commonly called benign (or acute) lymphocytic chorio-meningitis. Clinically it must be differentiated especially from tuberculous meningitis, from poliomyelitis, from epidemic encephalitis, and from the encephalitis that occasionally occurs as a sequel of various other virus diseases such as mumps and vaccinia. A positive diagnosis can be made by demonstrating the virus in the spinal fluid at the onset of the disease by inoculation into mice or guinea pigs. It may also be made by demonstrating protective power in the serum late in convalescence. One of these procedures is necessary since many cases showing this clinical picture fail to show the virus in the cerebrospinal fluid and do not develop protective power, and presumably are due to some other etiological agent.

The wide distribution of the disease is shown by the fact that Armstrong demonstrated protective power in the serum of six individuals from widely separated sections of this country. Furthermore Findlay, Alcock and

[3] Armstrong, C., and Lillie, R. D.: Experimental lymphocytic chorio-meningitis of monkeys and mice produced by virus encountered in studies of the 1933 St. Louis encephalitis epidemic, Pub. Health Rep., 1934, xlix, 959.

[4] Scott, T. F. McN., and Rivers, T. M.: Meningitis in man caused by a filterable virus, Jr. Exper. Med., 1936, lxiii, 397.

[5] Traub, E.: Filterable virus recovered from white mice, Science, 1935, lxxxi, 298.

Stern [6] recovered the same virus from cases of human infection and from mice in England. It is not certain whether man or the mouse constitutes the primary reservoir of infection, but it is believed to be man. Further study will probably show that the disease is more common than the number of reported cases would suggest. Recognition is important, particularly from the standpoint of prognosis, although the occurrence of severe and even fatal cases must be recognized.

[6] FINDLAY, G. M., ALCOCK, N. S., and STERN, R. G.: Virus aetiology of one form of lymphocytic meningitis, Lancet, 1936, i, 930.

REVIEWS

Body Water. By JOHN P. PETERS, M.D. viii plus 405 pages; 16 × 23 cm. Charles C. Thomas, Springfield, Illinois. 1935. Price, $4.00.

In spite of the extensive literature covered in "Body Water," this monograph can hardly be regarded as a general review of the water balance. No mention is made, for example, of the total water content of the body or of the distribution of fluid in various organs. Dr. Peters has quite frankly limited himself to those phases of this broad subject in which he and his co-workers have been particularly interested. The book might best be described as a critical analysis of some of the basic problems pertaining to the exchange of fluid in man. The author has clearly made a determined effort to see just how far the known facts can be explained by physico-chemical laws, and failing to find a satisfactory explanation on this basis, he stretches neither facts nor laws for the sake of reaching definite conclusions. Unfortunately, the result of this searching attitude seems to be a book in which the reader finds it difficult to extricate the facts from the discussions.

"Body Water" begins with a detailed discussion of the "chemical forces involved in exchange of fluid and solutes." One-third of the book is then devoted to the internal fluid exchange, following which there are two chapters on "Water of oxidation and the losses of water and solute through the skin and respiratory passages" and "Alimentary exchanges." The remaining third of the book is concerned entirely with the kidney.

Dr. Peters does not hesitate to deal harshly with existing theories. For example, he launches a vigorous campaign against the views of Drinker and Field on the mechanism of lymph formation. Contrary to the opinion of these authors, he also contends that the amount of protein in tissue fluid is small as compared to that present in lymph. In reviewing the chemical data on cerebrospinal fluid, Dr. Peters finds inadequate support for the hypothesis that this fluid is a simple ultrafiltrate of serum. Recent evidence discrediting the once popular theory of "bound water" is also cited.

The first chapter on osmotic pressure is in certain respects misleading. Osmotic pressure is simply an expression of the difference in diffusion pressure of the solvent in different parts of the system, and not due to a tendency of the solutes to expand as Dr. Peters seems to imply by the following statement: "The solutes which exert pressure in a solution are restrained by the boundaries of the fluid system in which they may be dissolved. Changes of the volume of the system cannot be effected by direct expansion of the solutes as they are in gases but only by the addition of solvents. . . ." The emphasis here is upon the solute whereas in reality the only part that the solute plays in the phenomenon is that of "diluting" the solvent.

The discoursive nature of many sections of "Body Water" makes it rather difficult reading for those chiefly interested in general information. This characteristic of the book, however, is perhaps not due so much to the author's method of presentation as to the complexities of a subject in which many of the fundamental facts are still lacking. A more didactic treatment would in many instances be unjustified and serve only to give the erroneous impression that general agreement existed on questions which are far from settled.

M. I. G.

A Mind Restored. By ELSA KRAUCH. 242 pages; 14.5 × 21 cm. G. P. Putnam's Sons, New York. 1937. Price, $2.50.

This book, bearing an introduction by William Seabrook, author of "Asylum" and of various travel tales, is another account of the experiences of a man suffering mental illness which required hospitalization. The tale describes the development of

a common type of depression which gradually progressed to the point that this man was unable to care for his own affairs, lost his business, went through a "rest home," a small, private sanatorium of the type which is unhappily not uncommon and finally had himself voluntarily admitted to a state hospital. After a period of months in the state hospital he made a social recovery and in the course of the next two years feels that he has recovered completely. Certainly he is again apparently a useful, self-supporting member of society and one who has learned a great deal from the experiences he lived through. Most of the book is devoted to his experiences in and reactions to the state hospital.

During the past several years there have been a number of such tales intended for general reading, designed to allay some of the fears which exist about mental disease and about conditions which are popularly supposed to exist in our institutions. A great many physicians find these books of the better type useful in demonstrating to their patients that other people suffer the same experiences and in giving the patient's family some allegedly inside information. This is one of the best of such books. It gives a fairly satisfactory, objective account of life in a state hospital. It is not Pollyannish, neither is it bitter. It will probably be a good book for selected depressive patients, particularly middle-aged groups and for families to read. It is one of the few books of this type which can be recommended for this purpose.

H. M. M.

Allergic Diseases: Their Diagnosis and Treatment. By RAY M. BALYEAT, M.A., M.D., F.A.C.P., Assisted by RALPH BOWEN, B.A., M.D., F.A.C.P. Fourth Edition. xv plus 516 pages. F. A. Davis Company, Philadelphia. 1936. Price, $6.00.

In the preface to the first edition of this work, the author states that it is written primarily to teach patients "concerning the possible causes of their trouble so that they may acquaint themselves more thoroughly with the animal and plant life with which they are surrounded, as products from one or both of them frequently cause their attacks." In the preface to the present edition, he revises this, stating that it has not been written for those doing special work in allergy, but for the general practitioner.

In attempting to estimate the usefulness of the volume, its content seems to be too voluminous and detailed for a patients' manual, and, at least in part, too elementary to be very useful to the physician. Thus, there seems to be no very good reason for the inclusion in a patients' handbook, of detailed directions for the intratracheal administration of iodized oil, nor should the patient be familiar with the technic of collection, staining, and examination of nasal secretions. Though an effort has been made to keep the terminology simple enough to be understood by the intelligent layman, technical expressions, without adequate explanation, are frequently used. The physician who expects much help in the treatment of patients, will probably be disappointed in the complete lack of detail as to methods of hyposensitization by hypodermic administration of atopens. The omission of a discussion of constitutional treatment reactions, and the author's statement that they do not occur (p. 225) are surprising.

On the whole, however, this volume is easy to read, interesting, and, at times, valuable. The section on botany is very helpful, well illustrated, and contains a number of pollen maps. Directions to patients for the elimination of offending substances should be useful.

T. N. C.

Diseases of the Nose and Throat. By C. J. IMPERATORI and H. J. BURMAN. 16 × 23 cm.; 723 pages. J. B. Lippincott Company, Philadelphia. 1935.

This new work on the diseases of the nose and throat is one that can be used by both senior medical students and practitioners alike. The volume consists of 52 chapters and 480 illustrations, covering 723 pages. It begins by giving a detailed description of office equipment and arrangement. This is followed by an outline of history taking and methods of examining the patient.

A review of the anatomy and physiology is presented, followed by discussion of the various affections of the nose and throat. One is accustomed to having etiology and pathology presented early in the discussion of a disease, but the authors have preferred to present first the symptoms, then the diagnosis, treatment (medical and surgical), pathology, complications, etiology, and prognosis in the order named.

The descriptions of operative technic are very clear and well illustrated.

A rather lengthy description of the diseases that can be diagnosed and treated with the aid of the bronchoscope and esophagoscope is included. A chapter is devoted to physical therapy methods in diseases of the nose and throat. Allergic manifestations in the upper respiratory tract are adequately discussed.

The style is very simple; it is one of the easiest of books to read. The type is large and the topics are arranged in somewhat the form of an outline. There are not a lot of unnecessary details to wade through, but at the same time nothing essential is omitted.

T. R. O'R.

Reports on Chronic Rheumatic Diseases. By THE BRITISH COMMITTEE ON CHRONIC RHEUMATIC DISEASES; Edited by C. W. BUCKLEY, M.D., F.R.C.P. 159 pages; 17 × 25 cm. Number one. 1936. The Macmillan Co., New York. Price, $4.00.

The stated purpose of this report by the British Committee on Chronic Rheumatic Diseases is to stimulate interest and research in the causes and treatment of rheumatic conditions and to develop more coördination of information and activities not only in Great Britain, but throughout the world.

The book is divided into three parts: the first includes a foreword, a description of the Committee organization, and a report of the Subcommittee on Nomenclature. A series of seven original articles on various phases and types of arthritis forms the second part; and four articles of review type constitute the third part. An extensive world-wide bibliography of articles written during 1936 completes the book; the arrangement of this section is by country, which gives one a better opportunity of comparing the activities of each nation.

The report of the Nomenclature Subcommittee is very interesting and is very detailed. It not only suggests a workable classification but explains its merits. The section on Clinical Criteria offers ample material for discussion and comparison of facts between the arthritis of known etiology and that of unknown. A careful and complete collection of all facts and features of each type is presented in apposing columns.

The original articles present material of much interest and value. The section called Critical Commentaries offers a review of the important international literature of the year and in general summarizes the feature articles from many countries and from different branches of medicine and surgery.

The report as a whole makes very interesting and instructive reading and tends to carry out its basic idea, namely to stimulate international coördination of thought and action in so important a disease. It may well be studied by student, practitioner and specialist.

A. F. V.

COLLEGE NEWS NOTES

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Books

Dr. Benjamin Warren Black (Fellow), Oakland, Calif., "Medical Policies and Procedures for the Resident Staff of the Alameda County Hospitals and Clinics";
Dr. Russell L. Haden (Fellow), Cleveland, Ohio, "Dental Infection and Systemic Disease";
Dr. Wingate M. Johnson (Fellow), Winston-Salem, N. C., "The True Physician: The Modern 'Doctor of the Old School'";
Dr. N. Thomas Saxl (Fellow), New York, N. Y., "Pediatric Dietetics";
Col. Harold W. Jones, M.C., U.S.A., "The Centenary of the Army Medical Library";
Dr. Frank H. Krusen (Associate), Rochester, Minn., "Light Therapy";
Dr. Charles Solomon (Associate), Brooklyn, N. Y., "The Traffic in Health."

Reprints

Dr. George C. Anglin (Fellow), Toronto, Ont., Canada—4 reprints;
Dr. Cornelius O. Bailey (Fellow), Los Angeles, Calif.—1 reprint;
Comdr. J. H. Chambers (Fellow), M.C., U.S.N.—1 reprint;
Dr. Ralph Oakley Clock (Fellow), New York, N. Y.—1 reprint;
Dr. George W. Covey (Fellow), Lincoln, Nebr.—1 reprint;
Dr. H. F. Crawford (Fellow), Memphis, Tenn.—1 reprint;
Dr. N. S. Davis, III (Fellow), Chicago, Ill.—4 reprints;
Dr. John Kenneth Deegan (Fellow), Ithaca, N. Y.—1 reprint;
Dr. Elliott B. Edie (Fellow), Uniontown, Pa.—1 reprint;
Dr. Harold G. F. Edwards (Fellow), Shreveport, La.—6 reprints;
Dr. John T. Farrell, Jr. (Fellow), Philadelphia, Pa.—3 reprints;
Dr. A. Allen Goldbloom (Fellow), New York, N. Y.—2 reprints;
Dr. George Alexander Gray (Fellow), San Jose, Calif.—1 reprint;
Dr. Jacob Gutman (Fellow), Brooklyn, N. Y.—1 copy, eleventh supplement to "Modern Drug Encyclopedia";
Dr. C. L. Harrell (Fellow), Norfolk, Va.—2 reprints;
Dr. James W. Hunter, Jr. (Fellow), Norfolk, Va.—2 reprints;
Dr. Henry J. John (Fellow), Cleveland, Ohio—11 reprints;
Dr. Joseph E. Knighton (Fellow), Shreveport, La.—3 reprints;
Dr. L. Winfield Kohn (Fellow), New York, N. Y.—3 reprints;
Dr. Maurice Kovnat (Fellow), Staten Island, N. Y.—1 reprint;
Dr. Charles A. LaMont (Fellow), Canton, Ohio—1 reprint;
Dr. H. Beckett Lang (Fellow), Brentwood, N. Y.—2 reprints;
Dr. George M. Levitas (Fellow), Westwood, N. J.—1 reprint;
Dr. Philip B. Matz (Fellow), Washington, D. C.—5 reprints;
Dr. James L. McCartney (Fellow), Catskill, N. Y.—1 reprint;
Capt. K. C. Melhorn (Fellow), M.C., U.S.N.—1 reprint;
Dr. M. A. Mortensen (Fellow), Battle Creek, Mich.—1 reprint;
Dr. Henry Monroe Moses (Fellow), Brooklyn, N. Y.—1 reprint;
Dr. Frederick W. Mulsow (Fellow), Cedar Rapids, Iowa—3 reprints;

Dr. Hilton S. Read (Fellow), Atlantic City, N. J.—1 reprint;
Dr. Rafael Rodriguez-Molina (Fellow), San Juan, P. R.—3 reprints;
Dr. William J. Ryan (Fellow), Pomona, N. Y.—1 reprint;
Dr. F. Janney Smith (Fellow), Detroit, Mich.—1 reprint;
Dr. Norman Strauss (Fellow), New York, N. Y.—1 reprint;
Dr. William Henry Wash (Fellow), Chicago, Ill.—4 reprints;
Dr. Morris Deitchman (Associate), Youngstown, Ohio—1 reprint;
Dr. William Freeman (Associate), Worcester, Mass.—1 reprint;
Dr. Barnett Greenhouse (Associate), New Haven, Conn.—1 reprint;
Dr. George B. Lake (Associate), Waukegan, Ill.—3 reprints;
Dr. William G. Leaman, Jr. (Associate), Philadelphia, Pa.—3 reprints;
Dr. Aleksei A. Leonidoff (Associate), Poughkeepsie, N. Y.—1 reprint;
Dr. David J. Sandweiss (Associate), Detroit, Mich.—3 reprints;
Dr. Albert Weinstein (Associate), Nashville, Tenn.—1 reprint.

Dr. Carl H. Gellenthien (Fellow), Valmora, N. M., presented a lecture on "The Diagnosis and Differential Diagnosis of Pulmonary Tuberculosis" before the Diagnostic Clinic and Fifteenth Annual Assembly of Twin Lakes District Medical Society at Burns' Alhambra Pavilion, Twin Lakes, Rockwell City, on June 17.

Dr. B. S. Pollak (Fellow), Secaucus, N. J., sailed on July 31 for Lisbon, Portugal, to attend the bi-annual Conference of the International Union Against Tuberculosis, which will be held at Lisbon September 5 to 9.

Dr. Edward E. Cornwall (Fellow), Brooklyn, N. Y., read a paper on "Diet and Longevity" before the American Therapeutic Society at its annual meeting held at Atlantic City, June 4.

The following Fellows of the College were selected as speakers in connection with the tenth annual Graduate Fortnight, presented by the New York Academy of Medicine, from November 1 to 12:
Dr. George Baehr, New York, N. Y., "The Pathology of Nephritis";
Dr. Robert F. Loeb, New York, N. Y., "Clinical Aspects of Nephritis";
Dr. Herman O. Mosenthal, New York, N. Y., "Clinical Aspects of Hypertension, Including Malignant Hypertension."

Dr. Homer Davis (Fellow), Genoa, Nebr., has been elected President-Elect of the Nebraska State Medical Association.

At the recent annual meeting of the North Carolina State Tuberculosis Association, held in Southern Pines, Dr. Paul A. Yoder (Fellow), Winston-Salem, N. C., was elected President of the Association.

Dr. Roland A. Davison (Fellow), Tucson, Ariz., has been appointed Medical Director of the Desert Sanatorium, succeeding Dr. Louis B. Baldwin (Fellow), Tucson, Ariz.

Dr. Alphonse McMahon (Fellow), St. Louis, Mo., was elected President of the American Therapeutic Society at its annual meeting held in Atlantic City in June.

Dr. F. M. Pottenger (Fellow, Regent, and Past President) presided as President at the meeting of the Association for the Study of Internal Secretions, held at Chalfonte-Haddon Hall, Atlantic City, June 7 and 8, 1937. His presidential address was on the subject of "Early History of the Association for the Study of Internal Secretions." Dr. Pottenger had previously served as President of the Association during the term 1935–1936, and was Secretary of the Association during the years 1917 to 1935.

Dr. Pottenger also gave an address on the evening of June 4, at the meeting of the American Therapeutic Society in Atlantic City. His subject was "The Clinical Versus the Public Health Point of View in the Treatment of Tuberculosis."

Dr. George W. McCoy (Fellow), former director of the National Institute of Health, Washington, D. C., has been assigned by the U. S. Public Health Service to make a study of leprosy in continental United States and the island possessions.

Dr. John E. Gordon (Fellow), field director of the International Health Division of the Rockefeller Foundation, New York, has been appointed professor of preventive medicine and epidemiology at Harvard University Medical School.

Dr. Austen Fox Riggs (Fellow and Life member) received an honorary degree of Doctor of Science from Williams College, Williamstown, on June 21, 1937.

Dr. Edgar M. Dunstan (Fellow) has resigned as Medical Director of Baylor Hospital to become Superintendent of the Dallas City County Hospital System.

Dr. Fred M. Meixner (Fellow) Peoria, Illinois, represented the National Tuberculosis Association of the United States at the meeting of the British National Association for the Prevention of Tuberculosis at Bristol, England, July 1, 2, 3. He addressed the conference on "Nutrition and Environment in Open Air Schools" and also on "Dispensary Methods."

OBITUARIES

DR. MUNFORD SMITH

Dr. Munford Smith (Fellow) of Los Angeles, California, died of cerebral thrombosis June 28, 1937 aboard the Motor Ship Canada bound for Panama. Dr. Smith had left with Mrs. Smith for the ocean trip as part of a convalescence from a recent period of ill health.

Dr. Smith was born December 3, 1892, in Pittsburgh, Pa. He had his early education there and at Bucknell College. He received his medical degree from the University of Maryland in 1919. That same year he became associated with the Barlow Sanatorium which association he held at the time of his death. He was Medical Director of the Sanatorium for the past ten years. Dr. Smith was active in many organizations. He was a member of the Los Angeles County, California State and American Medical Associations, the California Tuberculosis Association, a director of the National Tuberculosis Association and President of the American Sanatorium Association. He was an able and popular man, active and interested in his work with many friends both in and out of the profession who greatly miss him and his activities.

EGERTON L. CRISPIN, M.D., F.A.C.P.

DR. C. L. SHERRILL

Dr. Coite Long Sherrill (Fellow), of Statesville, North Carolina, the son of Walter and Anna Long Sherrill, was born September 4, 1887, in Texas. He received his academic education at Wake Forest College, N. C., and graduated in medicine at the North Carolina Medical College in Charlotte in 1914. He spent his internship at the Stetson Hospital, Philadelphia, and pursued post-graduate studies in several New York Hospitals, the Mayo Clinic, and various other clinics of the country.

Entering the U. S. Army in November, 1917, he was commissioned a captain, promoted to his majority in May, 1918, and sailed for France in August of that year. He was discharged July 19, 1919, as a lieutenant colonel, later entering the Medical Reserve Corps as a full colonel, which commission he held at the time of his death. He was very active in Legion affairs, was local Post Commander for one term, and held various executive offices with the state department of the Legion. He was elected National Commander of the Wildcat Division in 1936.

He was chief of the medical department of the H. F. Long Hospital, Statesville, N. C., at the time of his death, June 24, 1937, of coronary occlusion. His medical societies embraced his local and state medical societies, the American Medical Association; and he was made a Fellow of the American College of Physicians in 1931. For several years he had served as a member of the Postgraduate Committee of the N. C. State Medical Society;

and at the last meeting of this society he was also made Chairman of this Committee as well as Chairman of the Section on Medicine.

In 1917 he married Miss Mary McLain, and leaves three living children in addition to his widow. He was a member of the Methodist Church, and was considered a leading spirit in the affairs of his community. His hobby was fishing. While not given to writing or publication, he was a faithful attendant of the medical societies to which he belonged, an earnest student of medicine, a hard worker, and a fine gentleman who will be missed by all who knew him.

C. H. Cocke, M.D., F.A.C.P.,
Governor for N. C.

DR. WILLIAM WALLACE BEHLOW

Dr. William Wallace Behlow (Fellow), Lieutenant Commander, Medical Corps, United States Navy, retired, died April 29, 1937, at the Palo Alto Hospital, Palo Alto, California.

Dr. Behlow was born in San Francisco April 8, 1886. He was a graduate of Leland Stanford University, receiving the degree of A.B. in 1907. In 1912 he received the degree of M.D. at Harvard University, following which he interned at the Boston City Hospital. Following his internship he returned to California where he practiced his specialty, internal medicine, and served on the Faculty of the Medical School of the University of California.

On the declaration of war in 1917, Dr. Behlow patriotically gave up his private practice of medicine and enrolled in the United States Naval Reserve in the provisional grade of Assistant Surgeon. He reported for active duty at the Navy Yard, Mare Island, California on May 26, 1917. Following this he took the professional examination for entrance into the Medical Corps of the Navy and he was commissioned an Assistant Surgeon in the regular service dating July 19, 1917. In April, 1918, Dr. Behlow reported on the destroyer *U. S. S. Taylor* for duty at sea, and in 1919 he was transferred to the battleship *U. S. S. Idaho* as junior medical officer with the present Surgeon General of the Navy. This was followed by duty at the Recruiting Station, Salt Lake City, Utah, and an assignment with the Second Base Force, U. S. Marines, San Diego, which was followed by a tour of duty with the Bureau of Medicine and Surgery in the Personnel section. His next assignment was to the hospital ship *U. S. S. Relief*. From this duty he went to the United States Naval Hospital, Brooklyn, New York, where he was later hospitalized and finally placed on the retired list. Following retirement he reëstablished his residence in San Francisco, California.

Dr. Behlow was commissioned a Passed Assistant Surgeon with the rank of Lieutenant, U. S. Navy, on June 6, 1920. He was commissioned Surgeon with the rank of Lieutenant Commander, U. S. Navy, on June 4, 1925 and he was placed on the retired list on December 1, 1931.

Dr. Behlow was a very high type of medical officer professionally and personally, and was regarded as an outstanding internist among his colleagues. He was noted particularly as a specialist on contagious diseases. He was unmarried.

P. S. Rossiter, M.D., F.A.C.P.,
Governor for United States Navy.

DR. PETER JURJENS POTHUISJE

Dr. Peter Jurjens Pothuisje (Fellow), of Denver, Colorado, died June 4, 1937.

Dr. Pothuisje was born in Holland on February 27, 1866 and was naturalized at Seattle, Washington, about 1887. He received his pre-medical training at DePauw University and his medical training at the University of Ohio, graduating in 1893. At various times he pursued postgraduate work in Chicago and New York City.

Dr. Pothuisje was Consultant in Internal Medicine to St. Joseph's Hospital since 1910, to St. Luke's Hospital since 1922, to St. Anthony Hospital since 1906, and to Beth Israel Hospital since 1923. He was on the active service of the Denver General Hospital. He was a member of the Medical Society of the City and County of Denver, the Colorado State Medical Society, and the American Medical Association, and had been a Fellow of the American College of Physicians since 1924. During the World War, he served with rank of First Lieutenant U. S. A.

Dr. Pothuisje is survived by his wife, Lois Renette Tabor Pothuisje, and by two daughters, Lois, the wife of Dr. Ivan W. Philpott, of Denver, and Lucille, the wife of Mr. Lawrence Stubbs, of Wichita, Kansas.

Dr. Pothuisje was an able internist, devoting special attention to gastroenterology. He was a beloved family physician and those who knew him have suffered a great loss.

Gerald B. Webb, M.D., F.A.C.P.,
Governor for Colorado.

DR. VAUGHAN LE ROY SPRENKEL

Dr. Vaughan Le Roy Sprenkel (Associate), Allentown, Pennsylvania, died June 18, 1937, at the Jefferson Hospital, Philadelphia, as a result of a cerebral accident terminating a chronic state of purpura hemorrhagica.

Vaughan Sprenkel was born in Perkasie, Pa., in 1906. He attended the Public Schools of Perkasie, York and Allentown and completed his premedical education at Muhlenberg College, Allentown. He graduated, with honors, from the Jefferson Medical College, Philadelphia, in 1931. Dr. Sprenkel's internship was served at the Sacred Heart Hospital, Allentown, and in June 1932 he married and began his professional practice in Allentown.

Tragedy entered his life when his young bride died, in 1933, as the result of a complication after childbirth but, like the brave man he ever proved to be, Dr. Sprenkel sublimated his grief and sorrow by attempting to help others.

To write the obituary of a physician who lived but 31 years and whose professional life was, as a consequence of its brevity, very largely preparation for a future of work must give one pause.

Those intimately associated with Vaughan Sprenkel are aware that from boyhood he was a practical idealist and, as he matured, he selected the profession of medicine as an agency of altruistic and unselfish service to others.

After receiving his medical degree and completing his internship Dr. Sprenkel planned and executed an admirable course of postgraduate instruction.

His routine visits to Philadelphia hospitals kept him informed concerning the scientific work of a medical center and his enthusiasm, industry and earnestness brought him to the attention of those deeply interested in the progress and future of honorary scientific and medical associations.

Dr. Sprenkel became an Associate Fellow of the College in 1935. He was the youngest member of the International Association of Medical Museums and was, also, one of the youngest men to be selected for the honor of membership in the American Therapeutic Society. Dr. Sprenkel's brief professional career was successful in the highest and best sense of that much abused term.

He had learned in his student and interne days that the profession of Medicine must ever remain an Art, with a sound basis of Science and from the day he entered practice he was wisely far more interested in his patients than in the disease they were suffering from. Dr. Sprenkel was admired and loved by those who knew him best and the medical profession and our College has suffered a serious loss in the too early passing of this talented young physician.

E. J. Beardsley, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania.

MINUTES OF THE BOARD OF GOVERNORS

ST. LOUIS, MO.

April 19, 1937

The first meeting of the Board of Governors of the American College of Physicians, held in connection with the Twenty-first Annual Session, St. Louis, Mo., was called to order at 5:05 p. m., April 19, 1937, at the Jefferson Hotel, with Dr. Charles H. Cocke, Chairman, presiding and the following Governors, or their representatives, present, and with Mr. E. R. Loveland acting as secretary of the meeting: Dr. Fred W. Wilkerson, Dr. H. P. Mills (representing Dr. W. Warner Watkins), Dr. Turner Z. Cason, Dr. Glenville Giddings, Dr. James G. Carr, Dr. C. W. Dowden, Dr. E. H. Drake (representing Dr. Edwin W. Gehring), Dr. Henry M. Thomas, Jr., Dr. G. W. F. Rembert, Dr. Louis H. Fligman, Dr. R. W. Mendelson (representing Dr. LeRoy S. Peters), Dr. J. R. Scott (representing Dr. Walter W. Palmer), Dr. A. B. Brower, Dr. T. Homer Coffen, Dr. Charles T. Stone, Dr. Louis Warfield (representing Dr. Rock Sleyster), Dr. James F. Churchill, Dr. G. B. Gilbert (representing Dr. Gerald B. Webb), Dr. Wallace M. Yater, Dr. Samuel E. Munson, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Maurice C. Howard (representing Dr. Adolph Sachs), Dr. Allen A. Jones, Dr. Leander A. Riely, Dr. E. L. Bortz (representing Dr. E. J. G. Beardsley), Dr. Clement R. Jones (representing Dr. E. Bosworth McCready), Dr. J. Owsley Manier, Dr. Louis E. Viko, Dr. W. E. Ogden (representing Dr. Jabez H. Elliott), Dr. Oliver C. Melson, Dr. Clarence K. Canelo (representing Dr. Ernest H. Falconer), Dr. Joseph E. Knighton, Dr. Henry R. Carstens, Dr. Edward L. Tuohy, Dr. A. Comingo Griffith, Dr. H. W. N. Bennett (representing Dr. Robert B. Kerr), Dr. Clarence L. Andrews, Dr. Charles H. Cocke, Dr. C. F. Gormly (representing Dr. Alexander M. Burgess), Dr. Kenneth M. Lynch, Dr. J. Morrison Hutcheson, Dr. Charles E. Watts, Dr. Walter E. Vest, Dr. D. Sclater Lewis, Dr. Perceval S. Rossiter, Dr. Thomas Parran and Dr. Edgar V. Allen (Adviser to Dr. E. L. Tuohy).

Chairman Cocke declared those attending the meeting as alternate Governors were automatically seated, if their credentials had been presented to the Executive Secretary, or to him.

Abstracted Minutes of the preceding meetings of the Board of Governors at the 1936 Session were read, and, upon resolution, were approved.

At this point, Chairman Cocke recognized the President of the American College of Physicians, Dr. Ernest B. Bradley, who addressed the Board. He especially stressed the efficient aid the Governors had given to the College, and especially to the Committee on Credentials during the past year.

Chairman Cocke then reported upon the deliberations of the Board of Regents at its earlier meeting. He referred particularly to two amendments, one to the Constitution and one to the By-Laws, which had been considered by the Board of Regents at their December, 1936, meeting and subsequently published in the "Annals of Internal Medicine." These amendments related to limitations in the membership outside of Internal Medicine and to new standards of admission. He said that after more mature thought and study, the judgment of the Board had been that the amendments should not be presented at the present time, on which there would be a further report at the General Business Meeting of the College.

Chairman Cocke also referred to the matter of the Governors being the guests of the Regents during the past two or three years at the opening of the Annual Sessions, and expressed the hope that the Board of Governors might do something a little more concrete than just extend formal thanks.

On motion by Dr. Allen A. Jones, seconded and unanimously carried, it was

RESOLVED, that the Board of Governors extend to the Board of Regents an invitation to Dinner at the opening of the 1938 Session.

Secretary Loveland was called upon to present communications, whereupon he reported that he had received many letters from Governors who were unable to be present, several appointing others to act in their stead.

Chairman Cocke read to the Governors the list of candidates for Associateship and Fellowship who had been elected by the Board of Regents on April 18, and reported that their names would be posted on the Bulletin Board, where every one could consult the list.

Chairman Cocke then presented the list of Associates who were subject to being dropped for failure to qualify for Fellowship in the five-year period. The list had been reported to all the Governors concerned by the Executive Secretary, but each Governor was now given an opportunity to make any supplementary report before definite action had been taken by the Board of Regents.

Dr. C. W. Dowden requested information as to how an Associate so dropped might later qualify for Fellowship. The Executive Secretary reported that there had been but two cases that had come up as precedents. In one case the Associate had not qualified for Fellowship because of serious illness. He was later permitted to be proposed directly for Fellowship and not required to serve another five-year term as an Associate. The other case also had some extenuating circumstances connected with it, with the result that the candidate was considered directly for Fellowship as a special case. However, there must be adequate reason for such special consideration.

Chairman Cocke then presented the list of members who were subject to being dropped for two years' delinquency. This list also had been previously circulated among the Governors, so that every one was informed. Every one on the delinquent list had been advised on many occasions of his delinquency, and the Executive Secretary now felt there was no further action that could be taken, other than to proceed with the provisions of the By-Laws. Various members on the list were discussed, and no changes were made.

Dr. Cocke then reported upon the eighteen additions to Life Members since the last meeting, making a total of seventy-eight. He also reported upon the acquisition of the new College Headquarters, describing its architecture, location, facilities, etc., and invited the members of the Board to visit the headquarters whenever they are in Philadelphia.

Dr. Wilkerson, Governor for Alabama, proposed that the meetings of the College be so arranged as not to conflict with the meetings of the Alabama State Medical Association. There was general discussion of the time of the meetings, but it was pointed out that it is impossible to arrange the meetings of the College without some State society in some part of the country later selecting the same time. Chairman Cocke, however, said that the program committee took every possible step to avoid conflicts.

Dr. E. L. Tuohy, Governor for Minnesota, inquired as to how much credit is given to the character of histories and autopsies presented by candidates. Chairman Cocke replied that all histories and autopsies presented by candidates are examined by the Committee on Credentials to determine if they give evidence of careful preparation, proper history taking, proper laboratory studies, and correlation and discus-

sion of findings and diagnosis. He pointed out that the Committee on Credentials not infrequently returns histories which they feel have been delegated to secretaries or internes. Dr. Cocke further pointed out that candidates are also judged from other standards, such as the presentation of publications, theses or proof of certification by one of the national certifying boards.

Dr. Tuohy then recommended that the American College of Physicians should resort also to some sort of a report from the hospitals in which candidates are doing their work. This would act as an indirect means of inducing candidates to be more diligent and to more carefully observe the rules and regulations of the institutions. These sorts of inquiries, in addition to the presentation of histories, theses, etc., would give a further line-up on the character and qualifications of the candidates.

Chairman Cocke agreed to convey this suggestion to the Committee on Credentials, and suggested to Dr. Tuohy that he also discuss the matter with the Chairman of this Committee.

In further discussion of the matter, it was pointed out that the superintendent of some hospitals is a nurse, whereupon the suggestion was made that these inquiries should be sent to the Chief of Staff.

Dr. Robert M. Moore, Governor for Indiana, made a further suggestion that candidates who have recently changed from a large center to a small center should be given a period of time to become established before being considered for membership. The small city presents some obstacles to the continued restriction of practice to Internal Medicine, and some delay in accepting such candidates may afford a period of observation to determine whether they will be eligible in the new location.

Chairman Cocke then requested all members of the Board of Governors to join the Convocation procession on the evening of April 21.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF GOVERNORS

ST. LOUIS, MO.

April 21, 1937

The second meeting of the Board of Governors of the American College of Physicians, held in connection with the Twenty-first Annual Session, St. Louis, Mo., was called to order at 12:50 p. m., April 21, 1937, at the Jefferson Hotel, with Dr. Charles H. Cocke, Chairman, presiding, and Mr. Loveland acting as secretary. The roll call disclosed the following Governors, or their representatives, present: Dr. H. P. Mills (representing Dr. W. Warner Watkins), Dr. Turner Z. Cason, Dr. Glenville Giddings, Dr. James G. Carr, Dr. C. W. Dowden, Dr. E. H. Drake (representing Dr. Edwin W. Gehring), Dr. G. W. F. Rembert, Dr. Louis H. Fligman, Dr. R. W. Mendelson (representing Dr. LeRoy S. Peters), Dr. A. B. Brower, Dr. T. Homer Coffen, Dr. Charles T. Stone, Dr. Louis Warfield (representing Dr. Rock Sleyster), Dr. James F. Churchill, Dr. Wallace M. Yater, Dr. Samuel E. Munson, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Maurice C. Howard (representing Dr. Adolph Sachs), Dr. Allen A. Jones, Dr. Leander A. Riely, Dr. E. L. Bortz (representing Dr. E. J. G. Beardsley), Dr. J. Owsley Manier, Dr. Louis E. Viko, Dr. W. E. Ogden (representing Dr. Jabez H. Elliott), Dr. Oliver C. Melson, Dr. Clarence K. Canelo (representing Dr. Ernest H. Falconer), Dr. Joseph E.

Knighton, Dr. Henry R. Carstens, Dr. E. L. Tuohy, Dr. A. Comingo Griffith, Dr. Clarence L. Andrews, Dr. Charles H. Cocke, Dr. C. F. Gormly (representing Dr. Alexander M. Burgess), Dr. J. Morrison Hutcheson, Dr. Charles E. Watts, Dr. Walter E. Vest and Dr. D. Sclater Lewis.

Chairman Cocke thanked the alternate Governors for attending the Session and the meetings of the Board.

Upon motion by Dr. C. W. Dowden, seconded by Dr. A. B. Brower, and regularly carried, it was

RESOLVED, that the reading of the Minutes of the preceding meeting of the Board of Governors be dispensed with.

Chairman Cocke reported on the preceding meetings of the Board of Regents, mentioning particularly the following items:

(1) The Board of Regents has determined to appoint a Committee on Exhibits and Advertising to make a thorough survey, and to report back upon standards for raising the character and type of exhibits at the Annual Sessions and the type and character of advertising accepted in the ANNALS OF INTERNAL MEDICINE;

(2) The Board of Regents has appointed a Committee to formulate plans for a Revolving Fund to be available for Associates of the College to pursue postgraduate work to adequately qualify themselves for the examinations of the American Board of Internal Medicine;

(3) The Board of Regents has appointed a Committee on Postgraduate Education to organize courses of from two to four weeks, either preceding or immediately following the Annual Sessions of the College; these courses to be available to Fellows and Associates of the College at minimum cost. These postgraduate courses will be organized in connection with the next Annual Session of the College. They will cover every branch of Internal Medicine. In view of the fact that the College always holds its Annual Sessions in large medical centers, exceptional postgraduate facilities will be available;

(4) The Board of Regents has appointed a Consulting Committee to work with the Executive Secretary in connection with the publication of the 1937 Directory of the College; this Committee to have power in determining how Fellows and Associates shall be listed, and to designate what specialties and sub-specialties shall be recognized in the Directory.

In the discussion that followed, it appeared to be the consensus of opinion that the Board of Governors favor listing Fellows and Associates in the same section of the Directory, and not in separate sections as heretofore. A suggestion was made that under the geographical index, the names of Fellows should be listed first and the names of Associates should be listed immediately thereunder.

On motion by Dr. C. W. Dowden, seconded by Dr. O. C. Melson, it was

RESOLVED, that the above recommendation be communicated to the Committee on the Directory and to the Board of Regents.

On motion by Dr. C. W. Dowden, seconded by Dr. O. C. Melson, and regularly carried, it was

RESOLVED, that a transcript of the discussion by the Board of Governors be transmitted to the Consulting Committee on the Directory. (Full discussion is recorded verbatim in the Executive Secretary's office.)

There was a general discussion of the postgraduate courses to be offered by the College, it being pointed out that the courses are distinctly for members of the College, that the courses would be furnished at a very much lower cost than they are available elsewhere. Dr. Vest suggested that the courses should be made available also to candidates for membership.

Upon motion by Dr. Holt, seconded by Dr. Dowden, it was

RESOLVED, that the Board of Governors recommend to the Board of Regents that the postgraduate courses extend over a period of not less than two weeks and possibly up to a period of a month.

The Executive Secretary distributed mimeographed copies of the financial reports for the year 1936, and then proceeded to answer questions and explain various details related thereto.

Chairman Cocke called for a discussion among the Board of Governors of the subject "allied specialties" as it now appears in the Constitution and By-Laws of the College.

Dr. Griffith moved and Dr. Melson seconded the following motion:

RESOLVED, that the Board of Governors recommend to the Board of Regents the retention in the Constitution and By-Laws of the words "and allied specialties."

The motion was opened for discussion, Dr. Cocke explaining that "allied specialties" refer to pediatrics, neurology, psychiatry, pathology, tuberculosis, pharmacology, dermatology, bacteriology, roentgenology and public health. He explained further that the retention of these specialties within the scope of the College would continue to make available to the College the results of the investigations by men in these specialties.

Dr. Cason, Governor for Florida, expressed the opinion that the allied specialties should be eliminated. For example, he pointed out that the pediatricians have their own society and their own certifying board, the same being true in some of the other allied specialties, such as roentgenology. He felt that practitioners of the allied specialties would attend the meetings of the College less and less.

Dr. Breed, Governor for Massachusetts, expressed the opposite opinion, saying that he felt it would be suicidal for the College to restrict itself to the term Internal Medicine. The allied specialties should be retained within the By-Laws, and the gastroenterologists, dermatologists, etc., should be discouraged from setting up their own certifying boards.

Dr. Munson, Governor for southern Illinois, expressed the opinion that those engaged in the allied specialties who are interested in the College should be retained, and that programs of clinics should be provided to retain their interests.

Dr. Carr, Governor for northern Illinois, expressed the opinion that in keeping the pre-clinical men in the College, the College not only is showing respect for them, but will eventually obtain the help of men who are doing the most work along investigative lines. He said it would be a tragedy to eliminate from his part of Illinois those who are working continually and doing investigative work. The professors of physiology, bacteriology and pathology, and their associates in the medical schools of Chicago, are a decided asset to an institution like the College. They are called upon whenever a study of the fundamentals of medicine are desired. Such men had given him valuable help in the conduct of the Chicago program of the College.

Dr. Andrews, Governor for New Jersey, pointed out that whether the College membership is restricted to Internal Medicine or not, the program committee is free to invite surgeons, pathologists, or any others, to give papers and to participate in the clinics. He expressed the opinion that he favored the time when members of the College could say that the American College of Physicians is restricted to Internal Medicine.

Dr. Dowden, Governor for Kentucky, pointed out that the difficulty in the proposition under discussion had arisen in an effort to properly define the word "internist." In further discussion, he distinctly favored the retention of the "allied specialties" within the College. Many of those practicing allied specialties need a higher knowledge of Internal Medicine than many others who practice Internal Medicine exclusively.

Chairman Cocke pointed out that certification by the American Board of Internal Medicine should not be construed as being synonymous with Fellowship in the American College of Physicians. Membership in the College may mean much more than mere certification, because other considerations would enter into the matter of Fellowship than mere certification.

After further discussion of the definition of membership in the American College of Physicians, the question was put to a vote and the resolution unanimously adopted.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary